RECORD AND BRIEFS

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No. 17-___

IN THE
Supreme Court of the United States

MERCK SHARP & DOHME CORP.,
Petitioner,

v.

DORIS ALBRECHT, ET AL.,
Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Third Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In *Wyeth v. Levine*, 555 U.S. 555 (2009), this Court held that the FDA's approval of a drug label does not, standing alone, insulate the manufacturer from failure-to-warn liability under state tort law. At the same time, the Court recognized that if "the FDA would not have approved" the label demanded by state law, then the manufacturer could invoke an "impossibility" preemption defense. *Id.* at 571.

In this case, it was "undisputed" that (i) "the FDA was aware of the possible link" between petitioner's drug and the risk at issue; (ii) petitioner "submitted a comprehensive safety update to the FDA reporting ... numerous studies" finding "such an association"; (iii) petitioner "proposed warning language" about this risk, but the FDA "rejected" it; (iv) the FDA stated that the "conflicting nature of the literature d[id] not provide a clear path forward" and that it needed "more time" to consider "the issue of a precaution"; and (v) only later, after a report from a task force, did the FDA become "confident" that an association "potentially" existed. Pet.App.59a-60a.

The Third Circuit nonetheless held that a jury could find that petitioner had not shown by "clear and convincing evidence" that the FDA would have rejected a warning label of the type that respondents claim state law required. *See* Pet.App.37a, 56a-57a.

The question presented is: Is a state-law failure-to-warn claim preempted when the FDA rejected the drug manufacturer's proposal to warn about the risk after being provided with the relevant scientific data; or must such a case go to a jury for conjecture as to *why* the FDA rejected the proposed warning?

PARTIES TO THE PROCEEDING AND RULE 29.6 STATEMENT

Petitioner is Merck Sharp & Dohme Corporation, a wholly owned subsidiary of the entity formerly known as Schering Plough Corporation, which has been renamed Merck & Co., Inc. No publicly held corporation owns 10% or more of the stock of Merck & Co., Inc.

Respondents—identified by name and Third Circuit docket number in Appendix G (Pet.App.203a-224a)—are more than 500 plaintiffs who brought state-law failure-to-warn claims against Merck, alleging that they were injured by Merck's drug Fosamax prior to September 14, 2010. The Third Circuit resolved their appeals in one consolidated opinion. Pet.App.1a n.*. Pursuant to this Court's Rule 12.4, Merck files this consolidated petition to challenge the Third Circuit's decision.

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INTRODUCTION

Wyeth v. Levine, 555 U.S. 555 (2009), rejected an argument that the FDA's mere approval of a drug's label immunizes the manufacturer from any state tort liability for failure to warn. Rather, only if the FDA would have *rejected* a warning should the manufacturer be shielded from liability for failure to give it. In the latter scenario, it would truly be impossible to comply with both federal law (blocking the warning) and state law (mandating the warning). In *Levine*, however, there was no evidence that the FDA had paid more than "passing attention" to the risk at issue; no evidence that the drug manufacturer had provided the FDA with "evaluation or analysis" of the risk; no evidence that the manufacturer had "attempted to give the kind of warning" demanded by the plaintiff; and no evidence that the FDA had ever "made an affirmative decision" against allowing such a warning. *Id.* at 572-73.

In this case, by contrast, *each* of those factors is *undisputed*. Petitioner ("Merck") submitted data and analysis to the FDA suggesting that its Fosamax drug may be associated with certain bone fractures. Merck also proposed a warning addressing that risk. After back-and-forth, the FDA ultimately rejected the proposed addition, stating that it was not supported by the data. Pet.App.59a-61a. Despite all of this, the Third Circuit held that respondents' failure-to-warn claims were not legally preempted, because it believed that a *jury* could infer that the FDA's objection had been only to Merck's *wording*, and thus, as a "hypothetical" matter, that the agency might have approved the warning had it merely been phrased slightly differently. Pet.App.67a-68a.

Unfortunately, the decision below is not unique in its hostility to preemption. Despite *Levine*'s recognition that preemption would be appropriate if the FDA would have rejected the label demanded by the plaintiff, courts have erected a series of procedural and substantive hurdles to this defense, making it virtually impossible to establish, certainly as a matter of law. This case presents a particularly extreme illustration, with the court inventing a "clear and convincing evidence" standard exclusively for drug manufacturers, demanding "smoking gun" proof of *why* the FDA had rejected Merck's on-point warning, and leaving a lay jury to speculate about the intent of a federal regulatory authority.

This Court should grant certiorari to revive failure-to-warn branded drug preemption in the wake of the lower courts' interpretation of *Levine*. If a drug manufacturer candidly brings a risk to the FDA's attention and proposes an on-point warning, the FDA's rejection should suffice as a matter of law to preempt claims alleging failure to warn of that risk. By demanding more, courts have effectively eliminated impossibility preemption in this context: Even if manufacturers engage in good faith with the agency, propose a relevant warning, and follow the FDA's instructions, they remain on the hook based on a lay jury's psychoanalysis of *why* the agency had blocked compliance with state law. That untenable approach is of great importance, as proliferating tort suits stifle innovation, raise drug costs, undercut the FDA's role, and ultimately hurt public health. And this case is a perfect vehicle, because its undisputed facts would allow it to serve as an exemplar of when the preemption defense is legally established.

OPINIONS BELOW

The district court's opinion granting judgment to petitioner (Pet.App.113a-52a) appears at 2014 WL 1266994. The Third Circuit's decision vacating and remanding (Pet.App.1a-95a) was reported at 852 F.3d 268.

JURISDICTION

The Third Circuit entered judgment on March 22, 2017, and denied petitioner's timely motion for rehearing and rehearing en banc on April 24, 2017. *See* Pet.App.1a, 159a. On June 23, 2017, Justice Alito extended the time to file a certiorari petition until August 22, 2017. *See* No. 16A1264. This Court has jurisdiction under 28 U.S.C. § 1254(1).

PROVISIONS INVOLVED

Relevant statutory and regulatory provisions are reproduced at Pet.App.177a-202a.

STATEMENT

This case is about whether a brand-name drug manufacturer may be held liable for failure to warn about a health risk associated with its drug—even when the manufacturer brought that specific risk to the FDA's attention and proposed adding a warning about it to its label, only to have the FDA reject that proposal. The court below held that Merck *could* be liable under those circumstances. Although the FDA had rejected Merck's proposed warning and doubted that the data supported it, the Third Circuit ruled that a *jury*—speculating about hypotheticals—could find that it was *possible* that the FDA *would have* approved a warning had Merck altered its wording slightly (something the FDA never suggested).

A. Regulatory Background

Congress and the FDA have crafted a regulatory regime in which name-brand drug manufacturers and the agency work hand-in-hand to appropriately warn consumers of the risks inherent in using many beneficial medications. While "the manufacturer bears responsibility for the content of its label at all times," *Levine*, 555 U.S. at 570-71, the FDA also plays a central role in label approvals and revisions.

The FDA may approve a new drug "only if it determines that the drug in question is safe for use under the conditions of use prescribed, recommended, or suggested in [its] proposed labeling." *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2471 (2013). After approval, the FDA continues to monitor the drug and its label. The manufacturer must investigate and report serious, unexpected adverse events to the FDA within 15 days of receiving information about them, *see* 21 C.F.R. § 314.80(c)(1)(i), and each year it must report all "significant new information ... that might affect the safety, effectiveness, or labeling of the drug" to the agency, *id.* § 314.81(b)(2)(i).

Once a name-brand drug and its label have hit the market, there are only two ways in which that label may be revised by the manufacturer. *First*, the manufacturer may submit to the FDA a Prior Approval Supplement ("PAS"), asking for permission to change the label. *See generally id.* § 314.70(b). *Second*, through the Changes Being Effected ("CBE") regulations, a manufacturer may implement certain label changes subject to later FDA approval. *See id.* § 314.70(c)(6). Either way, the FDA's approval is required by federal law.

Because excessive warnings "could discourage appropriate use of a beneficial drug" and "decrease the usefulness and accessibility of important information by diluting or obscuring it," 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008), any revision to a label must meet specified scientific criteria. To justify a change to the "Warnings & Precautions" portion of a label, there must be "reasonable evidence of a causal association" between the drug and the health risk. 21 C.F.R. § 201.57(c)(6)(i). And to justify a change to the "Adverse Reactions" section, there must be "some basis to believe there is a causal relationship." *Id.* § 201.57(c)(7). These standards apply equally to changes brought about through the CBE process and to changes requested in a PAS. *See* 73 Fed. Reg. 49603, 49604-05 (Aug. 22, 2008).

Under statutory amendments not in force at the time of *Levine*, the agency has its own obligations too: It may not sit on its hands if it comes to believe that an existing label does not sufficiently warn against possible risks. If the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," it "shall promptly notify" the manufacturer, 21 U.S.C. § 355(o)(4)(A), who must "submit a supplement proposing changes to the approved labeling" or else "detail[] the reasons why such a change is not warranted," *id.* § 355(o)(4)(B). Just as importantly, the FDA may not let disagreement between it and the manufacturer about the need for (or proper content of) new warnings stand in the way of public health. If it "disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the

[agency] *shall initiate discussions to reach agreement* on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes." *Id.* § 355(o)(4)(C) (emphasis added). After those discussions, the agency "may issue an order directing [the manufacturer] to make such a labeling change as the [FDA] deems appropriate to address the new safety information." *Id.* § 355(o)(4)(E).

B. Fosamax and Its Label

1. Merck's drug Fosamax prevents and treats osteoporosis in postmenopausal women. Like the other bisphosphonates whose chemical properties it shares, Fosamax works by slowing the deleterious process that occurs in the bones of post-menopausal women, thereby helping patients retain bone mass, maintain bone strength, and avoid fractures. Pet.App.5a-6a. In one study, it reduced the risk of hip, spine, and wrist fractures by roughly 50%, and the risk of all symptomatic fractures—that is, ones that cause pain—by 26%. C.A.App.1103, 1699.

By interfering with this deleterious process, however, drugs like Fosamax could "theoretically increase" the risk of very rare "atypical femoral fracture[s]"—fractures in a very specific part of the femur (just below the hip joint ("subtrochanteric") or in the long part of the thigh bone ("diaphyseal")), that occur with only minimal trauma. Pet.App.12a; C.A.App.1118. In effect, it is alleged that the drug "may inhibit microdamage repair," C.A.App.1773-74, leading to small cracks in the bone (sometimes known as "stress fractures"), which could in turn progress into full-blown atypical femoral fractures. Pet.App.7a.

2. Merck and the FDA have long worked hand-in-hand to ensure that Fosamax's label reflects the best, current state of knowledge about the possible risk of atypical femoral fractures.

When Fosamax first hit the market in the mid-1990s, the FDA did not require any warning about this risk, even though Merck's scientists and others had discussed it with the agency. Pet.App.12a-13a. Since then, Merck has continually provided the FDA with the latest information about the potential connection. *E.g.*, C.A.App.1808, 1810-1929, 1938-68, 2576-31, 2696-2960 (materials submitted by Merck).

In March 2008, Merck submitted a safety update with "over 30 pages of information regarding atypical femur fractures and suppression of bone turnover," noting that "recent publications" "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures." Pet.App.14a. By June 2008, the FDA told Merck and other manufacturers that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." *Id.* Merck then "promptly complied" with a request for any further information. *Id.*

While the FDA "was analyzing Merck's data," Merck submitted a PAS proposing to add language to the Warnings & Precautions and Adverse Reactions sections of Fosamax's label, addressing the fractures that the FDA considered a "developing safety signal." *Id.* Based on nine articles and an analysis of fractures in Fosamax users, Merck contended that although it was then "not possible" to establish that Fosamax "increases the risk" of these fractures, it

was "important to include an appropriate statement" on the label to "increase physicians' awareness of possible fractures ... and allow early intervention," thereby "possibly preventing the progression to complete fracture." Pet.App.15a.

Accordingly, Merck proposed the following language for the Warnings & Precautions section:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Pet.App.15a-16a. At the same time, Merck proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions section of the label. Pet.App.16a.

3. Merck's submission kickstarted a back-and-forth with the FDA. In April 2009, an FDA official told Merck in a phone call that the FDA could "agree to add language in the Adverse Reactions section," but that Merck's "elevation of this issue to a precaution" was "prolonging review"; the FDA wanted to address the issue uniformly for "all bisphosphonates," but "the conflicting nature of the literature d[id] not provide a clear path forward." Pet.App.17a. Later that month, an FDA liaison sent Merck an email to the same effect: The "atypical fracture language" "could be approved" but "only" for the Adverse Reactions label, and Merck should "hold off" on changing the Warnings & Precautions label so that the agency and the industry could "decide on language" for a precaution, "*if it is warranted.*" Pet.App.17a-18a (emphasis added).

In May 2009, the FDA sent Merck a formal response authored by the same doctor from the April call. Pet.App.18a. The FDA approved the changes to the Adverse Reactions section—with a slight tweak in terms (Pet.App.18a)—but rejected the rest:

> While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels, your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been

> reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting.

Pet.App.18a-19a.

4. Almost a year later, the FDA told the public that the science had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." Pet.App.19a. None of the studies up to that date had concluded "even that Fosamax use was definitively associated with atypical fractures"; instead, they suggested only a "potential[]" increase in risk or that bisphosphonates "may be associated" with such fractures. Pet.App.13a. To resolve the issue, the FDA announced that it would work with an outside task force to gather more information. Pet.App.19a.

In September 2010, that task force reported that there appeared to be an "association between long-term bisphosphonate use and atypical fractures." Pet.App.20a. In October 2010, the FDA announced that while it was "'still not clear'" whether bisphosphonates *caused* these "'unusual femur fractures,'" they "'ha[d] been predominantly reported in patients taking bisphosphonates.'" Pet.App.21a. An agency official credited the task force's report for the agency's change in view, stating that the report made it "'confident' that atypical femur fractures are 'potentially more closely related to' long-term use of bisphosphonates" than the agency "'previously had evidence for.'" *Id.* (quoting C.A.App.1396). As a result, the agency declared that it would *now* be "considering label revisions." Pet.App.20a.

In October 2010, the FDA formally directed the manufacturers to revise the "Precautions" section of their labels. It admitted that it still was "not clear" whether bisphosphonates caused the fractures, as they "also occur" in those "who have not been treated with bisphosphonates." Pet.App.21a. Nonetheless, because the fractures might be related to long-term use of the drug, the FDA ordered revised labels. Pet.App.21a-22a. Those labels note that "[a]typical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients," that patients with certain symptoms should be "evaluated to rule out a femur fracture," and that doctors should consider "[i]nterrupt[ing]" bisphosphonate use for such patients. Pet.App.22a.

C. This Litigation

1. After the FDA's action, many Fosamax users who had allegedly suffered atypical femur fractures sued Merck. Though the details varied, the plaintiffs generally alleged that Merck failed to warn about this risk. Pet.App.23a-24a. Some 1200 cases were sent to a multi-district litigation ("MDL") proceeding in the District of New Jersey. Pet.App.23a.

After holding a bellwether trial, the district court addressed the cross-cutting issue of preemption. It recognized that impossibility preemption "'is a demanding defense,'" Pet.App.168a (quoting *Levine*, 555 U.S. at 573), but held that there was "clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label" before the September 2010 task force report. *Id.* The district court thus entered judgment for Merck on the claims of all plaintiffs who alleged injuries prior to that date. Pet.App.152a.

2. The Third Circuit vacated and remanded. It began by conceding that applying *Levine* is "not ... straightforward." Pet.App.28a. Its standard—that preemption is warranted if there is "clear evidence that the FDA would not have approved a change" to the label, 555 U.S. at 571—"is cryptic and open-ended, and lower courts have struggled to make it readily administrable." Pet.App.28a. *Levine* thus left "an anomaly in our preemption jurisprudence: the number of cases applying the clear evidence standard continues to grow, yet the clear evidence standard remains undefined." Pet.App.35a.

Without seeking any guidance from the FDA, the Third Circuit addressed this anomaly by adopting two rules. *First*, it held that *Levine*'s reference to "clear evidence" imposes a heightened standard of proof: To prevail on a preemption defense, "[t]he manufacturer must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence,'" which the court equated with the more familiar "clear and convincing evidence" test. Pet.App.36a, 37a. The defendant must prove it is "*highly probable*" that the FDA would have rejected the change. Pet.App.37a (emphasis added).

Second, the court held that the question whether the FDA would have rejected the proposed change is one for the jury, even when the historical facts are undisputed, because the question is "counterfactual." Pet.App.54a. A manufacturer thus cannot establish the preemption defense as a matter of law, pre-trial, absent a "'smoking gun' rejection letter from the FDA" that would leave a jury no choice but to find the state-law claim preempted. Pet.App.55a.

The Third Circuit found no smoking gun here. To be sure, it saw plenty of smoke. Prior to the task force report, the FDA had expressed doubt about the evidence tying bisphosphonate use to atypical femur fractures, including in rejecting Merck's proposed warning. Pet.App.59a-61a. Respondents thus had to show that the FDA spurned Merck's proposal because of unspecified semantic concerns with Merck's *wording*, not because it doubted the underlying data or need for a warning. Pet.App.61a-62a. That is highly dubious, because the FDA *is required to* "initiate discussions to reach agreement on whether the labeling for [a] drug should be modified" if it "becomes aware of new safety information." 21 U.S.C. § 355(o)(4)(A), (C). Indeed, the FDA had done just that when it tweaked Merck's proposed Adverse Reactions language.

Although the court did not "discount the force of this evidence," it concluded that a jury could still find it less than "highly probable" that the FDA would have rejected a differently phrased label change. Pet.App.62a, 63a. In its view, a juror could conclude that the FDA's rejection was indeed all about Merck's terminology (*viz.*, its use of the term "stress fractures"), with the agency refusing—in violation of its statutory duty—to offer alternate language. Pet.App.67a. Thus, "a reasonable jury applying a heightened standard of proof *could* conclude" that the FDA would have allowed the label change. *Id.*[1]

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[1] The Third Circuit also held that the plaintiffs adequately pleaded a distinct failure-to-warn claim: that Merck should have altered the Adverse Reactions section of its label earlier than it did. Pet.App.70a. That ruling is not at issue here.

REASONS FOR GRANTING THE WRIT

In view of "[t]he importance of the pre-emption issue" to the pharmaceutical industry upon which so many rely, *Levine*, 555 U.S. at 563, this Court has granted review to correct courts' unduly narrow understandings of the doctrine, even absent any circuit conflict. *E.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 610-11 (2011).

The Court should do the same here. The decision below illustrates the impossible position into which federal and state courts have forced brand-name drug manufacturers. Even if they cooperate with the FDA, share their safety data, and follow the agency's direction to "hold off" on adding label warnings, they *still* cannot escape costly, burdensome tort litigation complaining about those labels. Plaintiffs' lawyers, of course, can *always* dream up some "hypothetical" reason why the FDA might have rejected a proposed warning—and under the decision below, that suffices to reach a lay jury, which will be asked (case-by-case) to guess as to the reasons why the federal regulator blocked the manufacturer's state-law compliance.

This approach misunderstands *Levine*, conflicts with this Court's post-*Levine* precedents in *Mensing* and *Bartlett*, and threatens serious disruption to the cooperative relationship between the FDA and drug manufacturers. A jury's speculation about *why* the FDA blocked a manufacturer's effort to comply with state law cannot possibly defeat federal preemption. This petition is the ideal vehicle in which to lay down a legal marker for when a failure-to-warn claim *is* properly preempted in the branded drug context, and thus revive the preemption defense that courts since *Levine* have narrowed virtually out of existence.

I. THE LOWER COURTS HAVE MADE IT IMPOSSIBLE FOR BRAND-NAME DRUG MANUFACTURERS TO ESTABLISH PREEMPTION.

This Court warned in *Mensing* that preemption cannot be rendered "all but meaningless," 564 U.S. at 621, by forcing drug manufacturers to prove "counterfactual conduct of the FDA," *id.* at 623 (plurality op.). But the lower courts have defied that directive. In applying *Levine* to brand-name drugs, they have held the preemption defense out-of-reach by speculating as to counterfactuals, even when the record is clear that the FDA was aware of the risk and working with the manufacturer to address it. The decision below is the high-water mark of this trend, ruling that even though the FDA had rejected an on-point warning and cited inadequacies in the existing data, a jury could impose liability by "speculat[ing] about hypothetical scenarios" under a novel, heightened burden of proof. Pet.App.67a, 68a. All of this is quite wrong. No evidence of preemption could be more "clear" than the FDA's *actual rejection* of the warning required under state law.

A. States May Impose Liability for Failure To Warn Only If the FDA Would Have Allowed the Label Change.

This Court's leading decision on preemption for brand-name drug manufacturers is *Levine*, decided almost a decade ago. In that case, the majority held that the FDA's mere approval of a drug label did not, by itself, preempt state-law failure-to-warn liability. Rather, to show "impossibility" preemption, the drug manufacturer must show that it was *forbidden* by federal law from providing the additional warning—*i.e.*, that the FDA would have rejected it.

In *Levine*, the plaintiff successfully argued to the Vermont state courts that the label for Wyeth's drug Phenergan should have more strongly advised doctors to administer the drug indirectly through an IV-solution (the "IV-drip" method) rather than directly into the vein (the "IV-push" method). 555 U.S. at 560-63. On certiorari, this Court confronted the manufacturer's categorical contention that "the FDA's approvals [to Phenergan's labeling] provide[d] Wyeth with a complete defense" to the tort claims. *Id.* at 558. In Wyeth's view, "it would have been impossible for it to comply with the state-law duty to modify Phenergan's labeling without violating federal law," *id.* at 563, because it had no power to change its label without the FDA's permission.

The Court agreed in principle that, had federal law prevented Wyeth from updating its label, then Levine's failure-to-warn claim would have been preempted. *Id.* at 572. But the Court disagreed with that premise. The majority explained that, under the federal scheme, it is the manufacturer's duty to ensure that "its warnings remain adequate as long as the drug is on the market." *Id.* at 571. Through the CBE regulation, manufacturers may strengthen their existing warnings, even without the FDA's prior permission, provided they have good reason to do so. *See id.* at 569-71. Accordingly, the "mere fact that the FDA approved Phenergan's label" did not alone make compliance impossible, and so did not warrant preemption. *Id.* at 573; *see also id.* at 593 (Thomas, J., concurring in judgment) ("nothing in the ... regulatory scheme necessarily insulates Wyeth from liability under state law simply because the FDA has approved a particular label").

"Of course," the majority went on to admit, "the FDA retains authority to reject labeling changes," even when made "pursuant to the CBE regulation," "just as it retains such authority in reviewing all supplemental applications." *Id.* at 571. And if the FDA would have *rejected* the relevant change, that would certainly trigger preemption. *See id.* "But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements." *Id.*

Wyeth "offered no such evidence." *Id.* at 572. *First*, Wyeth did "not argue that it supplied the FDA with an evaluation or analysis" about "the specific dangers posed by [IV-push]." *Id.* at 572-73. *Second*, the record showed that neither the FDA nor Wyeth "gave more than passing attention to the issue." *Id.* at 572. *Third*, Wyeth "d[id] not argue that it attempted to give the kind of warning required by the Vermont jury," or that it had been "prohibited from doing so by the FDA." *Id.* *Finally*, the Vermont Supreme Court "concluded that the FDA had not made an affirmative decision to preserve [IV-push]" or against "strengthening [Wyeth's] warning about IV-push." *Id.* Given this utter paucity of evidence, the majority could not "credit Wyeth's contention that the FDA would have prevented it from adding a stronger warning." *Id.*

The general rule that emerges from *Wyeth* is, in theory, administrable: If the FDA would have allowed a stronger warning, then states may impose liability for the manufacturer's failure to provide one. But if the FDA would have rejected such a change, the failure-to-warn claim is preempted. *See id.*

B. In the Absence of Further Guidance, Courts Have Gutted the Preemption Defense That *Levine* Recognized.

In practice, however, *Levine*'s line has proved elusive. This Court need not take Merck's word for it. As the court below put it, *Levine* did not "explain how courts should apply" its "cryptic," "open-ended" standard, and "lower courts have struggled to make it readily administrable." Pet.App.28a, 33a. Other courts have also observed that *Levine* did not "define clear evidence," *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 457 (Mass. 2015), or "clarify what constitutes" it, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 391 (7th Cir. 2010). *Levine* did not indicate "the level of proof required" to demonstrate preemption, *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1270 (W.D. Okla. 2011), and so "lower courts are left to determine what satisfies this 'clear evidence' standard in each case," *Schilf v. Eli Lilly & Co.*, 2010 WL 3909909, at *4 (D.S.D. Sept. 30, 2010).

In short, while *Levine* was a good illustration of a case in which the manufacturer did *not* prove that the FDA would have rejected a labeling change, it gave the lower courts little help in determining when a drug manufacturer *has* proven that proposition. Without that guidance, and in the absence of an exemplar case from which to analogize, the state and lower federal courts have gradually shifted the line further and further in tort plaintiffs' favor, against preemption and expanding liability. Left to their devices, the courts have made proving impossibility preemption under *Levine* next to impossible. The Third Circuit's decision below epitomizes that shift, rendering the defense truly academic.

1. Procedurally, courts have interpreted the *Levine* majority's offhand, solitary reference to "clear evidence," 555 U.S. at 572, as imposing a uniquely high burden of proof, beyond the difficulty inherent in proving the impossibility of complying with both state and federal law.

The Seventh Circuit, for example, read *Levine* to limit preemption to cases in which the manufacturer "met the stringent standard of proving that there was *clear evidence* the FDA would have rejected the proposed change," *Mason*, 596 F.3d at 391, and held that the manufacturer had not made the "extensive showing required by *Levine*" because it did not "meet its burden of demonstrating by *clear evidence*" that the FDA would have rejected the proposed label, *id.* at 396 (emphasis added). Massachusetts' Supreme Judicial Court followed, setting out "*clear evidence*" as the required standard, *Reckis*, 28 N.E.3d at 457; referring to it *thirteen times*; and suggesting that it requires unusually strong proof of a virtually irrebuttable character, *see, e.g.*, *id.* at 460 n.29; *see also Dobbs v. Wyeth Pharm.*, 606 F.3d 1269, 1270 (10th Cir. 2010) (mem.) (remanding for application of *Levine*'s "new 'clear evidence' standard").

Substantively, these courts have effectively eliminated *Levine*'s preemption defense, requiring a manufacturer to prove that the FDA actually denied a request for a virtually identical label—*and* that it did so because it disagreed with the proposed label *as a matter of policy*, not for some other reason—to obtain judgment as a matter of law. Since the FDA does not always spell out its reasoning, this makes it all but impossible to avoid a trial in which the jury is left to speculate about the agency's thought process.

Reckis proves the point. There, the plaintiffs claimed that ibuprofen's label should have warned them—by name or by degree of dangerousness—about the risk of the "life-threatening disease" of toxic epidermal necrolysis ("TEN") and its more serious variant, Stevens-Johnson Syndrome ("SJS"). 28 N.E.3d at 454. However, a subsequent citizen's petition (which allows citizens to ask the FDA to strengthen a drug's label, *see* 21 C.F.R. § 10.25(a)) asked the FDA to warn that ibuprofen could cause "serious skin reactions" that "may progress to more serious and potentially life-threatening diseases, including ... [SJS] and [TEN]." 28 N.E.3d at 453. In response, the FDA ordered the label revised to warn of "severe skin reactions," but not to mention the life-threatening nature of those reactions or to identify SJS or TEN by name, noting that consumers who purchase ibuprofen off the shelf are unlikely to recognize those names. *Id.* at 453.

Nonetheless, the Supreme Judicial Court held that the plaintiffs' claims were not preempted insofar as they sought a warning of life-threatening risks. *See id.* at 456-60. Even though the citizen petition had expressly requested such a warning to no avail, the court hypothesized that the agency's refusal "could well have been merely a byproduct of its rejection of these requested warnings" because they mentioned the conditions by name. *Id.* at 459. That is, perhaps the FDA *would have* approved a warning that noted the risk of life-threatening reactions but omitted their names. Because the agency "provided no reasoning" for rejecting the life-threatening aspect of the warnings, it would be "speculative" to rely on its rejection to find preclusion. *Id.*

Other decisions have been similarly dismissive. In *Mason*, for example, the Seventh Circuit found no preemption even though the FDA thrice rejected calls to add risk of suicide to the label of another antidepressant from the same chemical category, and even though the FDA publicly stated that there was no evidence of increased suicide risk in adults three months *after* the 23-year-old victim took the medicine. 596 F.3d at 394-95. And in *In re Prempro Products Liability Litigation*, the Eighth Circuit spent all of a sentence rejecting a claim that the FDA would have rejected stronger warnings. 586 F.3d 547, 563 (8th Cir. 2009); *see Mason*, 596 F.3d at 391 n.1 (noting that *Prempro* rejected preemption "rather summarily"); *see also, e.g.*, *Gurley v. Janssen Pharm., Inc.*, 113 A.3d 283, 291-92 (Pa. Super. Ct. 2015) (no preemption because the proposed but FDA-rejected warning of "possible birth defects" mentioned as an example a different congenital malformation than one at issue); *Hutto v. McNeil-PPC, Inc.*, 79 So. 3d 1199, 1210 (La. Ct. App. 2011) (no preemption because the manufacturer "did not attempt to have all the warnings" the plaintiffs requested "included on its Infants' Tylenol® label").

Indeed, even the few cases in which courts *have* found preemption illustrate the heightened barriers courts have erected around that defense. In *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1095 (10th Cir. 2017), the plaintiffs asserted that the victim's parents should have been warned about the risk of birth defects when taking the fertility drug Clomid *prior* to pregnancy, not just *during* pregnancy. The Tenth Circuit assumed that, to prevail, Aventis had to show that "'no reasonable juror could conclude that it

[was] anything less than highly probable that the FDA would have rejected' the proposed label" in order for the manufacturer to prevail at summary judgment. *Id.* at 1099 (quoting Pet.App.59a). Aventis met that standard, but only because a prior citizen petition asking the FDA to alter Clomid's label had "presented arguments [that were] *virtually identical* to the Cervenys' [arguments]," and the FDA denied it *and* stated expressly that "the scientific literature did not justify ordering changes to the labeling that warn ... beyond those presently included." *Id.* at 1101. In other words, it is still possible to prevail on a preemption defense, but only if the FDA rejected a near-verbatim request *and* it expressly did so because it disagreed with that request as a matter of policy or science.

2. The decision below represents the high-water mark of lower courts' efforts to gut manufacturers' preemption defense, building on almost a decade of plaintiff-friendly caselaw misconstruing *Levine*.

Procedurally, the Third Circuit formalized the heightened evidentiary burden largely left implicit in cases like *Reckis*. The court squarely held that drug manufacturers "must prove that the FDA would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by 'clear evidence,'" a standard "synonymous" with the clear-and-convincing-evidence standard that the court called a "well-recognized intermediate standard of proof." Pet.App.35a-37a. The court defined "clear and convincing" evidence as evidence "'indicating that the thing to be proved is *highly probable* or *reasonably certain*.'" Pet.App.37a (emphases added) (quoting *Black's Law Dictionary* 674 (10th ed. 2009)).

The court further held that this standard must be applied by a jury, not by a judge. In its view, the *Levine* test requires a "counterfactual" analysis, "based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes." Pet.App.54a. The court admitted that this was a "complex" task, but concluded that "it does not require any special legal competence or training" and therefore "the question of whether the FDA would have approved a plaintiff's proposed warning is a question of fact for the jury." *Id.*

On that approach, a drug manufacturer is only entitled to judgment as a matter of law if *no* "*reasonable jury* could find it less than *highly probable* that the FDA would have rejected Plaintiffs' proposed warning." Pet.App.56a-57a (emphases added). As a practical matter, this leaves virtually no avenue for pre-trial relief, even if all the historical facts are undisputed. Absent a comprehensive, highly detailed rejection letter from the FDA, a plaintiff's lawyer could always chalk the agency's decision up to some idiosyncratic defect that the drug manufacturer could have remedied had it only tried harder or strung words together differently. And a jury, facing a sympathetic plaintiff, would not need much urging to reach such a finding, especially with the thumb that the "clear and convincing" standard places on the scales. This approach thus replaces the court, acting as gatekeeper and applying a rule of law, with a lay jury, invited to speculate case-by-case about why an expert federal agency did what it did.

The Third Circuit's heightened evidentiary standard—and its determination about the identity of the factfinder—bore fruit in its substantive result. The court acknowledged the myriad indications that the FDA would have rejected *any* additional warning about the connection between Fosamax and atypical femoral fractures before September 2010: Merck's submission of relevant data and proposed warning; the FDA's rejection and its statements asking Merck to "hold off" while it evaluated whether any warning was "warranted"; the agency's expressions of doubt about the strength of the data; and its convening of a task force, only *after* whose report the FDA ordered a label revision. Pet.App.59a-61a. All of these facts were "undisputed." *Id.*; *see supra* pp. 7-13.

The court also acknowledged the fundamentally bizarre claim at the heart of respondents' case. There was no dispute that the FDA had rejected Merck's attempt to strengthen its label. If it had done so because the agency did not believe that *any* warning was needed, then respondents' claims were plainly preempted. Their claims therefore hinged on the notion that the FDA had concluded that a stronger warning was needed regarding atypical femur fractures—in other words, that Merck had done the right thing by going to the FDA and seeking leave to amend its warning—but that the agency had inexplicably disregarded its statutory obligations and rejected Merck's supposedly deficient label outright based on a "language quibble" (Pet.App.61a), rather than work with Merck on a warning that would properly warn the public of the risk that all parties recognized (just as the agency had done for Merck's proposed Adverse Reactions label change).

Despite all of this, the court held that Merck could not satisfy the court's heightened burden of proof. It lacked the "smoking gun" needed to prevail as a matter of law because "a reasonable juror, looking at all the evidence and trying to reconstruct a hypothetical event, could conclude that it is less than highly probable that the FDA would have rejected the change." had it been "properly worded." Pet.App.56a, 62a-63a. In other words, even though the FDA *did* reject Merck's warning, the jury could conjecture about the FDA's reasoning and thereby conclude that the agency *would not have* rejected the warning had Merck improved its draftsmanship.

The upshot is this: Unless a plaintiff demands a warning nearly identical to one the FDA has already rejected—and rejected expressly on scientific rather than semantic or ambiguous grounds—state failure-to-warn claims are not preempted, no matter how hard a manufacturer tries to meet its obligations.

C. The Third Circuit's Decision Is Wrong.

On both procedure and substance, the decision below is flatly mistaken.

1. Take first its clear-and-convincing-evidence standard. In the past few years, this Court has twice reiterated that the preponderance of the evidence standard "is the standard generally applicable in civil actions, because it allows both parties to share the risk of error in roughly equal fashion." *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S. Ct. 1749, 1758 (2014); *see also id.* (entitlement to fees in patent cases need not be proven by clear and convincing evidence); *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1934 (2016) (misconduct for

purposes of enhanced patent damages need not be proven by clear and convincing evidence). In keeping with this strong default rule, this Court has applied a higher standard in civil litigation only where Congress has specified one, *see, e.g.*, *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 102-06 (2011), where courts have traditionally applied one, *see, e.g.*, *Radio Corp. of Am. v. Radio Eng'g Labs., Inc.*, 293 U.S. 1, 7-9 (1934), or where the Constitution demands one, *see, e.g.*, *Addington v. Texas*, 441 U.S. 418 (1979).

Whether the FDA would have rejected a label change for purposes of a preemption defense falls into none of these categories. Congress has not spoken to the issue; the Third Circuit identified no historical practice requiring heightened proof; and the Constitution does not demand any. While the parties "may be interested intensely in [this] civil dispute over money damages," it is not unique or important enough to trigger heightened standards of proof. *Santosky v. Kramer*, 455 U.S. 745, 755 (1982).

The Third Circuit did not address this wall of countervailing authority. Instead, it dissected the single sentence on this topic in *Levine*, concluding that in context "[t]he term 'clear evidence' [must] ... specif[y] how *difficult* it will be for the manufacturer to convince the factfinder." Pet.App.35a. But "the language of a[Supreme Court] opinion is not always to be parsed as though we were dealing with the language of a statute." *Reiter v. Sonotone Corp.*, 442 U.S. 330, 341 (1979). This Court would not upend the ordinary rules of civil litigation through a single sentence, especially in a case that did not present the issue because Wyeth offered "*no* such evidence." 555 U.S. at 572 (emphasis added). Rather, the Court was

simply restating the principle that preemption requires *actual* rather than *hypothetical* conflict. *See Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 884 (2000). As *Geier* thus instructed, "a court should not find preemption too readily in the absence of *clear evidence of a conflict*." *Id.* at 885 (emphasis added). *Levine* was just invoking that lesson, not creating a unique standard of proof from whole cloth.

The Third Circuit also reasoned that the Court has often used "clear evidence" to refer to a standard of proof. Pet.App.36a. However, those cases prove only that, when the Court *does* impose a heightened standard, it does so clearly and for good reason. *See Reno v. Am.-Arab Anti-Discrimination Comm.*, 525 U.S. 471, 489 (1999) (requiring "particularly demanding" proof of selective prosecution "[b]ecause such claims invade a special province of the Executive"); *Oriel v. Russell*, 278 U.S. 358, 362-63 (1929) (calling for "clear and convincing evidence" for orders to turn over property in bankruptcy because "[t]he proceeding is one in which coercive methods by imprisonment are probable and are foreshadowed"); *Microsoft*, 564 U.S. at 101 (adopting a heightened standard because Congress used the term "presumed valid," which had a "settled meaning in the common law" stretching back centuries). *Levine*'s stray use of "clear evidence," without any explanation of the compelling need for a departure from the ordinary rules, bears no resemblance to these cases.

Finally, the Third Circuit reasoned that its heightened standard flowed from the presumption against preemption. Pet.App.37a. This Court has explained, however, that it is "unusual" to "treat a presumption as alone establishing the governing

standard of proof"; presumptions generally establish who bears the burdens of production and persuasion. *Microsoft*, 564 U.S. at 103. Contrary to the Third Circuit's fears, this view still leaves preemption a "demanding defense," Pet.App.37a (quoting *Levine*, 555 U.S. at 573); manufacturers must, after all, show it was *impossible*, not merely difficult, to comply with both state and federal law.

2. The Third Circuit went further astray when it came to application of *Levine*'s substantive rule. There could hardly be clearer evidence that the FDA *would have* rejected a warning than the undisputed fact that the FDA *did* reject a warning. Yet even that is not sufficient for the court below, which would ask a *jury* to psychoanalyze *why* the agency did so, and reject preemption based on such conjecture.

In *Levine*, the majority pointed to a series of facts that precluded Wyeth from demonstrating that the FDA would have rejected a stronger warning: Wyeth had not "supplied the FDA" with data; neither Wyeth nor the FDA "gave more than passing attention to the issue"; Wyeth had not "attempted" to give a stronger warning; and the FDA had not made "an affirmative decision" to reject one. 555 U.S. at 572-73. Although *Levine* had no occasion to spell out which combinations of these facts would suffice, here *all of them* are *undisputed*. Pet.App.46a n.122. Merck raised the issue of atypical femoral fractures with the FDA, provided the agency with all available data, proposed a relevant warning, and was told to "hold off" because its justification was "inadequate." There is thus no factual dispute for a jury to resolve. If the factors *Levine* mentioned are relevant, then there *must* be preemption here, as a matter of law.

The court reasoned, however, that a jury could find that FDA rejected Merck's proposed warning because it objected to some of its particular *language* and not because it decided—as a policy matter—that a warning was inappropriate. Pet.App.64a-66a. Thus, a the FDA may have approved a *differently worded* warning compliant with state law. *Id.*

But this sort of conjecture by an inexpert lay jury cannot possibly defeat federal preemption. As this Court's post-*Levine* decisions make clear, preemption is not overcome by an attenuated chain of remote possibilities by which the defendant, hypothetically, could have reconciled conflicting state and federal duties. The generic drug manufacturers in *Mensing*, for example, could not independently revise their own labels, but could have lobbied the FDA to work with the name-brand manufacturer on a change. 564 U.S. at 616. Even if federal law *required* them to do so, the Court held that state failure-to-warn claims were preempted: It was "certainly possible that, had the [generic] [m]anufacturers asked the FDA for help, they might have eventually been able to strengthen their warning." *Id.* at 620. But such "conjecture[]" does not "suffice" to defeat preemption; otherwise, conflict preemption would be "all but meaningless." *Id.* at 621; *see also id.* at 623 (plurality op.) ("consider[ing] ... the contingencies inherent in these cases" would be "speculati[ve]" and inappropriate). *Bartlett* recognized a similar point when it held that some possibilities of reconciling conflicting state and federal obligations—such as "simply leaving the market"—are too extreme or hypothetical to defeat the preemption defense. 133 S. Ct. at 2478.

The Third Circuit's reasoning cannot be squared with these cases. It is "certainly possible" that the FDA's rejection of a warning proposed by a brand-name manufacturer could have been based on some non-scientific objection to the warning's terminology. And so it is also "certainly possible" that the FDA might, hypothetically, have approved a warning that used different verbiage. But as *Mensing* teaches, "certainly possible" does not defeat preemption. 564 U.S. at 620. Playing this "what if" game—in this context, by nitpicking the manufacturer's proposed warning in an effort to imagine an alternative basis for its rejection by the FDA—simply takes the notion of impossibility too far, rendering preemption "all but meaningless." *Id.* at 621. And asking a lay jury to conjecture case-by-case about "counterfactual[s]" like these (Pet.App.63a) offends the Supremacy Clause. If it is undisputed that the manufacturer gave the FDA the relevant data and proposed changing its label, that should suffice—as a matter of law—to preempt state tort liability for failure to warn.

II. This Is an Ideal Vehicle To Clarify the Legal Scope of a Critical Defense in an Important Area of Law.

This Court should step in to correct the errors discussed above, because of the importance of the preemption defense to the pharmaceutical industry, and because the approach reflected by the decision below threatens the cooperative regulatory process between the FDA and drug manufacturers. And this is an ideal vehicle for doing so, because the facts here would allow this case to be an exemplar to the courts of when failure-to-warn claims *are* preempted—a counterexample to *Levine*, so to speak.

A. An Unduly Narrow Preemption Defense Threatens the Pharmaceutical Industry and the FDA's Regulatory Role.

When it comes to policing the boundary between state tort law and federal regulation of prescription drugs, this Court has recognized the overwhelming importance of getting it right. In its recent cases in this area, it has generally granted review because of the "importance of the pre-emption issue," *Levine*, 555 U.S. at 563—and sometimes based on the FDA's request—not because of disagreement amongst lower courts, *e.g.*, Pet. for a Writ of Cert. in *Mensing*, 2010 WL 638478, at *19-*25; Pet. for a Writ of Cert. in *Levine*, 2007 WL 776723, at *13-*15.

This is for good reason. Each year, tens of thousands of plaintiffs sue drug companies in tort; indeed, this MDL alone embraces over one thousand. But, extended too far, state tort law undermines the FDA's expert judgment by substituting regulation by one lay jury after another (and potentially in conflict with one another). *See Levine*, 555 U.S. at 626 (Alito, J., dissenting) (warning against allowing "juries in all 50 States ... to contradict the FDA's expert determinations"). After all, "juries are ill equipped to perform the FDA's cost-benefit-balancing function," and only the expert agency "has the benefit of the long view." *Id.* Left unchecked, moreover, state tort law risks "whipsawing the medical community," *id.*, and thus jeopardizes access to safe and affordable medicines by "rais[ing] prices to the point where those who are sick are unable to obtain the drugs they need," *id.* at 582 (Breyer, J., concurring). Both the regulatory scheme and the public interest suffer when the scale is tilted too heavily toward plaintiffs.

The decision below tilts those scales in extreme fashion, and threatens those important interests. To start, the Third Circuit's approach inevitably will increase drug prices, because it puts manufacturers in an impossible spot: Even if they disclose every potential new risk to the FDA, and even if they seek to change their labels to account for those risks, they still face liability at the hands of a jury unless the FDA gives them definitive proof that it would have rejected every conceivable proposed change as a matter of policy. Most often, however, there is no such "smoking gun."

The Third Circuit's decision also undermines the FDA's regulatory authority. The court's clear-and-convincing-evidence standard means that even where it is more likely than not that the FDA *would have rejected* the plaintiff's demanded label change, the manufacturer cannot invoke preemption. By definition, then, the Third Circuit's test applies where the FDA would have made one policy decision, but a sympathetic jury evaluating an isolated case makes another, thus transferring regulatory power from the FDA to inexpert juries and their potentially conflicting findings. No one could think that this outcome embodies wise regulatory policy.

In addition, the decision below threatens to swamp the FDA and disrupt its relationship with the industry. If any hypothetical alternative, non-scientific basis for the agency's rejection of a proposed warning suffices to defeat preemption, then manufacturers will have no choice but to inundate the agency with alternative proposals, requests for clarification, and other attempts to smoke out its precise grounds. This Court has warned, however,

against liability rules that give regulated parties "an incentive to submit a deluge of information that the [FDA] neither wants nor needs," to the detriment of the agency and the public it protects. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001).

In short, the decision below will hurt not only the pharmaceutical industry, but the patients it serves and the agency that regulates its products (which has thus far not been asked to weigh in).

B. This Case Presents an Ideal Vehicle for Defining *Levine*'s Parameters.

As explained above, in the absence of guidance illustrating the kinds of facts that prove preemption under *Levine*, courts have construed the defense very narrowly, heaping up obstacles to manufacturers wishing to show that the FDA would have rejected the plaintiff's demanded label. *See supra* Part I.B.

This case presents an opportunity to turn the tide. The Third Circuit made clear that its decision turned on its interpretation of *Levine*'s statement about "clear evidence." It emphasized that the question before it was "not just whether a reasonable juror could find that the FDA would have approved [respondents'] proposed warning," but "whether a reasonable juror could find that it is *highly probable* that the FDA would have rejected the warning." Pet.App.58a (emphasis added). And it relied on that heightened standard to reverse the district court's judgment: Because a reasonable jury could "at least" conclude that it was not "highly probable" that the FDA would have "rejected [respondents'] proposed warning," summary judgment was inappropriate. Pet.App.63a; *see also, e.g.*, Pet.App.58a, 59a.

More importantly, this case would provide the Court with an excellent vehicle for putting another stake in the ground, across the field from *Levine*'s—this time to illustrate facts that *prove* preemption and to fashion an administrable rule of law that *protects* the Supremacy Clause. Merck presented compelling evidence on every front where Wyeth fell short. *See supra* p. 28. Indeed, the Third Circuit itself admitted that, even under its own heightened standard, this case was close. It did not "discount the force" of Merck's evidence about the FDA's actions, or doubt its "potential to sway a jury." Pet.App.62a. But because it demanded a "'smoking gun' rejection letter," and authorized the jury to speculate about the *basis* for the FDA's undisputed refusal to allow Merck to comply with state law, it refused summary judgment. Pet.App.55a, 67a.

If preemption does not exist as a matter of law here, it will rarely be found to exist anywhere. This Court should confirm that it does, and correct the ill-conceived course set by other courts post-*Levine*.

CONCLUSION

The petition should be granted.

AUGUST 22, 2017

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APPENDIX

APPENDIX A

PRECEDENTIAL

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

Nos. 14-1900 et al.*

IN RE: FOSAMAX (ALENDRONATE SODIUM)
PRODUCTS LIABILITY LITIGATION

On Appeal from the United States District Court
for the District of New Jersey
(D.C. Nos. 3:08-cv-00008-FLW *et al.*, MDL No. 2243)
District Judge: Honorable Joel A. Pisano

Argued June 30, 2016

Before: FUENTES, CHAGARES, and RESTREPO,
Circuit Judges

(Opinion Filed: March 22, 2017)

* This opinion applies to all appeals listed in Appendix A, attached.

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OPINION OF THE COURT

FUENTES, *Circuit Judge.*

Beginning in 2010, hundreds of plaintiffs filed personal-injury suits against the drug manufacturer Merck Sharp & Dohme, alleging that the osteoporosis drug Fosamax caused them to suffer serious thigh bone fractures. Each Plaintiff brought a state-law tort claim alleging that Merck failed to add an adequate warning of the risk of thigh fractures to Fosamax's FDA-approved drug label. Many Plaintiffs also brought a variety of additional claims including defective design, negligence, and breach of warranty.

Plaintiffs' suits were consolidated for pretrial administration in a multi-district litigation in the District of New Jersey. Following discovery and a bellwether trial, the District Court granted Merck's motion for summary judgment and dismissed all of Plaintiffs' claims on the ground that they were preempted by federal law. The District Court based its ruling on the Supreme Court's decision in *Wyeth v. Levine*,[1] which holds that state-law failure-to-warn claims are preempted when there is "clear evidence" that the FDA would not have approved the warning that a plaintiff claims was necessary.

We will vacate and remand. Preemption is an affirmative defense, and Merck has not carried its burden to prove that it is entitled to that defense as a matter of law. The *Wyeth* "clear evidence" standard is demanding and fact-sensitive. It requires the factfinder to predict a highly probable outcome in a

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[1] 555 U.S. 555 (2009).

counterfactual world and, therefore, requires a court sitting in summary judgment to anticipate both the range of conclusions that a reasonable juror might reach and the certainty with which the juror would reach them. Here, Plaintiffs have produced sufficient evidence for a reasonable jury to conclude that the FDA would have approved a properly-worded warning about the risk of thigh fractures—or at the very least, to conclude that the odds of FDA rejection were less than highly probable. Under *Wyeth* and Rule 56, that is enough for Plaintiffs to defeat summary judgment and proceed to trial.

I. BACKGROUND

A. Fosamax and Atypical Femoral Fractures

Fosamax is a drug manufactured by Merck that belongs to a class of drugs known as bisphosphonates. The Food and Drug Administration ("FDA") approved Fosamax in the 1990s for the treatment and prevention of osteoporosis in postmenopausal women.

Fosamax treats osteoporosis by correcting an imbalance in the so-called "bone remodeling" process. Throughout a person's life, bones are continuously broken down through a process called resorption and then reformed by the creation of new bone cells. In postmenopausal women, the rate of bone resorption exceeds that of bone formation, thereby causing bone loss. If bone loss continues unchecked, a person may develop osteoporosis, "a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and increases the risk of

fracture."[2] Bisphosphonates like Fosamax slow the resorption process, restoring the balance between resorption and formation and reducing the risk of osteoporotic fracture.

Plaintiffs claim, however, that Fosamax can actually increase the risk of certain bone fractures. They allege that by slowing resorption, bisphosphonates inhibit bone repair. According to Plaintiffs, bones frequently develop so-called "microcracks," which are ordinarily repaired through the resorption process. An accumulation of microcracks can lead to incomplete bone fractures called "stress fractures." The standalone term "stress fracture" typically connotes a fracture resulting from excessive loading of a normal bone, and is commonly seen in physically active individuals. A so-called "insufficiency stress fracture," by contrast, is a fracture caused by normal loading of poor-quality bone. Plaintiffs claim that while stress fractures typically heal on their own, "some Fosamax users who develop insufficiency fractures have reduced bone toughness, and Fosamax prevents the normal repair of the fracture."[3] According to Plaintiffs, these patients may then go on to develop what are known as "atypical femoral fractures": severe, non-traumatic, low-energy complete fractures of the femur.

Plaintiffs in this case are all Fosamax users who suffered atypical femoral fractures. They allege,

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[2] U.S. Dep't of Health & Human Servs., *Bone Health and Osteoporosis: A Report of the Surgeon General* 41 (2004).

[3] Pls. Br. 15 (citing A 884.)

among other things, that (1) Fosamax caused these atypical fractures by slowing the resorption process and allowing microcracks to accumulate. and (2) Merck was aware of the risk of such fractures but acted unlawfully by failing to warn doctors and patients of those dangers. They claim that Merck should have included a warning about atypical femoral fractures in the federally-mandated drug warnings that accompany prescription drugs. The interplay, and potential collision, between state-law warning duties and federal regulatory requirements is the subject of this appeal.

B. Regulatory Framework

The Food, Drug, and Cosmetic Act ("FDCA")[4] regulates the marketing and sale of prescription drugs in the United States. Under the FDCA, a manufacturer must obtain approval from the United States Food and Drug Administration ("FDA") before marketing a new drug.[5] As part of a new drug application, the manufacturer must submit a proposed package insert, commonly called the "drug label," that sets out the drug's medical uses ("indications") and health risks.[6] "To obtain FDA approval, drug companies generally must submit evidence from clinical trials and other testing that evaluate the drug's risks and benefits and demonstrate that it is safe and effective for all of the indications 'prescribed, recommended, or suggested'

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[4] 21 U.S.C. § 301 *et seq.*

[5] *Id.* § 355(a).

[6] 21 C.F.R. § 201.57(a); 21 U.S.C. § 355(b)(1)(F).

on the drug's label."[7] The FDA's approval of a new drug application is conditioned on its approval of the exact text of the drug label.[8]

Drug labels includes two sections relevant to this litigation: a "Warnings and Precautions" section and an "Adverse Reactions" section. The Warnings and Precautions section must describe "clinically significant adverse reactions," including any that are "serious even if infrequent."[9] The Adverse Reactions section requires a description of "the overall adverse reaction profile of the drug based on the entire safety database." including a list of all "undesirable effect[s]. reasonably associated with use of a drug."[10]

After a drug is approved, the FDA retains the authority to approve or require amendments to the drug's label.[11] The fundamental premise of the federal drug labeling scheme. however, is that "manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times."[12]

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[7] *In re Schering-Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239 (3d Cir. 2012) (quoting 21 U.S.C. § 355(d)).

[8] 21 C.F.R. § 314.105(b), (c).

[9] *Id.* § 201.57(c)(6)(i).

[10] *Id.* § 201.57(c)(7).

[11] 21 U.S.C. § 355(o)(4); 21; C.F.R. § 314.93; *see also Wyeth*, 555 U.S. at 567 (observing that the 2007 FDCA amendments "granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug's initial approval").

[12] *Wyeth*, 555 U.S. at 579; *see also* 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 amendments to the

The manufacturer is charged not only "with crafting an adequate label" as an initial matter, but also "with ensuring that its warnings remain adequate as long as the drug is on the market."[13]

A manufacturer can fulfill its responsibility to revise the warnings on a drug label in two ways.

First, the "Changes Being Effected" ("CBE") regulation permits a manufacturer to unilaterally change a drug label to reflect "newly acquired information," subject to later FDA review and approval.[14] Under the CBE regulation, the manufacturer may, upon filing a supplemental application with the FDA, change a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction"; it need not wait for FDA approval.[15] To add a warning to the Warnings and Precautions section through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence."[16] Thus, a

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FDCA "shall not be construed to affect the responsibility of the responsible person . . . to maintain its label in accordance with existing requirements").

[13] *Wyeth*, 555 U.S. at 571.

[14] 21 C.F.R. § 314.70(c)(6)(iii); *see also Wyeth*, 555 U.S. at 568 (discussing CBE amendment process).

[15] *Id.* § 314.70(c)(6)(iii)(A).

[16] 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008) (FDA notice regarding final amendment to CBE regulation); *see also* 21 C.F.R. 201.57(c)(6)(iii) (Warnings and Precautions section "must be revised to include a warning about a clinically significant

manufacturer can amend the label to address potential adverse effects even if the evidence for a causal connection would "not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[17]

For purposes of the CBE regulation, "newly acquired information" includes "new analyses of previously submitted data."[18] This definition "accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments."[19] Thus, if a manufacturer were to "determine[ ] that existing warnings were insufficient based on . . . a new analysis of previously submitted data, [it] could still submit a CBE based on its new analysis of the previous data."[20] A manufacturer's ability to change a label via the CBE process is not absolute, however. The FDA reviews CBE submissions and retains the power to reject proposed changes that do not meet the regulatory standards.[21]

Second, manufacturers can implement "major changes" to a label by filing a so-called "Prior

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hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.").

[17] 73 Fed. Reg. at 49,604.

[18] 21 C.F.R. § 314.3(b).

[19] *Wyeth*, 555 U.S. at 569.

[20] 73 Fed. Reg. at 49,606.

[21] *See* 21 C.F.R. § 314.70(c)(4)-(6).

Approval Supplement" ("PAS").[22] Unlike a CBE change, a PAS change requires prior FDA approval before it can be implemented.[23] The key distinction for present purposes is that a proposed label change that qualifies for a CBE supplement—including a proposal to "add or strengthen a contraindication, warning, precaution, or adverse reaction"— need not be submitted through the PAS process and does not require prior FDA approval.[24]

It is important to recognize, however, that the FDA does not simply approve warnings out of an abundance of caution whenever the manufacturer posits a theoretical association between drug use and an adverse event. As the FDA has recognized, "[e]xaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug."[25] Moreover, "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance."[26] Accordingly, the FDA will reject a PAS application or CBE amendment if there is insufficient evidence of a causal link between drug use and the adverse event.[27]

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[22] *Id.* § 314.70(b).

[23] *Id.* § 314.70(b)(3).

[24] *Id.* § 314.70(b)(2)(v)(A); *id.* § 314.70(c)(6)(iii)(A) .

[25] 73 Fed. Reg. 2848, 2851 (Jan. 16, 2008).

[26] *Id.*

[27] *Id.*

C. Fosamax Labeling History

Both Merck and the FDA have long been aware that anti-resorptive drugs like Fosamax could theoretically increase the risk of atypical femoral fractures. The question that both Merck and the FDA faced in the years following the drug's approval was whether the developing evidence of a causal link between Fosamax and atypical fractures was strong enough to require adding a warning to the Fosamax drug label. As explained further in Section II of this opinion, the primary question in this appeal is whether, prior to September 2010, the FDA would have rejected an attempt by Merck to unilaterally amend the Fosamax label (via a CBE submission) to include a warning about the risk of atypical femoral fractures. The following evidence bears on that question.

i. Early Studies Suggest a Possible Link Between Fosamax and Atypical Femoral Fractures

During Fosamax's development, Merck scientists and third-party researchers discussed the possibility that anti-resorptive drugs could inhibit a bone's ability to repair microdamage, potentially leading to stress fractures. In 1992, prior to FDA approval, Merck informed the FDA that "antiresorptive agents may inhibit microdamage repair by preventing . . . bone resorption at the sites of microdamage."[28] Nonetheless, when the FDA approved Fosamax in 1995 for the treatment of osteoporosis in postmenopausal women, it did not require Merck to

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[28] A 1774.

include a warning about bone fractures. Nor did it do so in 1997, when it approved Fosamax for the prevention of osteoporosis in postmenopausal women.

Between 1995 and 2010, scores of case studies, reports, and articles were published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures. Plaintiffs have directed our attention to six such studies from this period. None of these studies, however, concluded that Fosamax caused bone fractures, or even that Fosamax use was definitively associated with atypical fractures. Rather, they variously stated that Fosamax use "may . . . potentially" increase the risk of fracture[29] or "may be associated" with insufficiency fractures,[30] or that certain findings "raise[d] the possibility" that Fosamax use led to fractures.[31] Merck's assertion that the link between Fosamax and fracturing "remained hypothetical and unsubstantiated"[32] may be an understatement, but not even Plaintiffs suggest that there was definitive proof of a causal connection at this time.

Merck kept the FDA informed of these and other studies suggesting a possible association between bisphosphonates and fractures, either citing or submitting them in communications with the agency. In March 2008, Merck submitted a periodic safety

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[29] A 1258.

[30] A 1237.

[31] A 1243.

[32] Merck Br. 8.

update to the FDA that included over 30 pages of information regarding atypical femur fractures and suppression of bone turnover. Merck reported that "recent publications" had "implicated a link between prolonged bisphosphonate therapy and atypical low-energy non-vertebral fractures."[33] It also stated "the reporters related these findings to severely suppressed bone turnover that may develop during long-term" use of Fosamax.[34] Later that month, Merck forwarded to the FDA a letter published in the *New England Journal of Medicine* describing a "potential link between [bisphosphonate] use and low-energy fractures of the femur."[35]

In June 2008, the FDA informed Merck that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates."[36] It also stated that it was "concerned about this developing safety signal."[37] The FDA asked Merck to submit any investigations it had conducted or reports it had received regarding femoral fractures. Merck promptly complied.

ii. Merck Attempts to Amend the Fosamax Label

In September 2008, while the FDA was analyzing Merck's data, Merck submitted a PAS to the FDA. As discussed above, a PAS is a label-change request

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[33] A 2597.

[34] *Id.*

[35] A 1928-33.

[36] A 1935.

[37] *Id.*

that, unlike a CBE submission, requires prior approval from the FDA.[38] In the PAS, Merck proposed to add language to both the Warnings & Precautions and the Adverse Reactions sections of the label to address atypical femoral fractures. Merck explained that "[i]t is not possible with the present data to establish whether treatment with" Fosamax "increases the risk of [these] . . . low-energy subtrochanteric and/or proximal shaft fractures."[39] But because of the temporal association between these fractures and Fosamax use, Merck believed that it was "important to include an appropriate statement about them in the product label" to "increase physicians' awareness of possible fractures in some osteoporotic patients at risk and allow early intervention, thereby possibly preventing the progression to complete fracture and/or other complications."[40]

Merck proposed adding the following language to the Warnings and Precautions section of the label:

> **Low-Energy Femoral Shaft Fracture**
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area,

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[38] *See supra* Section I.B.

[39] A 1349.

[40] *Id.*

> often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.[41]

Merck also proposed adding "low-energy femoral shaft fracture" to the list of reported adverse reactions in the Adverse Reactions section of the label,[42] as well as the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh."[43] In support of its PAS application, Merck included an analysis of femur fractures in Fosamax users and cited to nine articles reporting cases of low-energy femoral fractures in Fosamax users.

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[41] A 1371.

[42] A 1383.

[43] A 2742.

In April 2009, Merck representatives held a telephone conversation with Dr. Scott Monroe of the FDA. According to Merck's internal notes, Dr. Monroe stated that the FDA could agree to add language in the Adverse Reactions section of the label, but that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review.[44] The FDA wanted "to approach the issue of a precaution from the [perspective] of all bisphosphonates" and was "working with the Office of Safety and Epidemiology to do so."[45] Dr. Monroe also stated that because "the conflicting nature of the literature does not provide a clear path forward, . . . more time will be need[ed] for FDA to formulate a formal opinion on the issue of a precaution around these data."[46]

Later in April 2009, an FDA liaison sent Merck an email stating that the FDA was not prepared to include language about low-energy femoral fractures in the Warnings and Precautions section of the label and would only approve a reference to atypical fractures in the "Adverse Reaction" section.[47] The FDA asked Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "then work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide

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[44] A 1970-71.

[45] A 1971.

[46] 46 *Id.*

[47] A 1498.

on language for a [Warnings and Precautions] atypical fracture language. if it is warranted."[48]

In May 2009. the FDA sent Merck a "Complete Response" letter. authored by Dr. Monroe. In the Complete Response, the FDA approved the addition of "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions section, but the FDA rejected Merck's proposed addition to the Warnings and Precautions section. Because the parties vigorously dispute the grounds for this rejection, it is worth excerpting the relevant portion of the FDA notice in full:

> We have completed the review of your [PAS] applications, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and our recommendation to address this issue.
>
> 1. While the Division agrees that atypical and subtrochanteric fractures should be added to the **ADVERSE REACTIONS, Post-Marketing Experience** subsections of the [Fosamax] labels. your justification for the proposed **PRECAUTIONS** section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available

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[48] *Id.*

literature and post-marketing adverse event reporting.[49]

The outcome of this case hinges in large part on how one reads (or really, on how a reasonable jury could read) this language in conjunction with the FDA's accompanying actions and communications. Plaintiffs claim that the FDA was objecting only to Merck's use of the imprecise and potentially misleading term "stress fractures," and that the FDA would have approved a proposed warning that specifically discussed the risk of atypical femoral fractures while eliminating the general references to stress fractures. Merck claims that this letter, along with the FDA's other communications, demonstrates that the FDA simply did not believe there was sufficient evidence of a causal link between Fosamax use and atypical fractures, and would have rejected *any* proposed warning relating to such a risk.

iii. The FDA Revises its Position on the Link Between Bisphosphonates and Atypical Femur Fractures

In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated publicly that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[50] The FDA announced that it would work with an outside expert task force to gather additional information.

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[49] A 1500-01.

[50] A 1508.

In September 2010, the task force published a report finding that "there is evidence of a relationship between long-term [bisphosphonate] use and a specific type of subtrochanteric and femoral shaft fracture."[51] The report stated that although there was an association between longterm bisphosphonate use and atypical fractures, the association had not been proven to be causal. The FDA responded by issuing a Drug Safety Communication stating that, "[a]lthough it is not clear if bisphosphonates are the cause [of fractures], these unusual femur fractures have been identified in patients taking these drugs."[52] Regarding the task force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports" and would be "considering label revisions."[53]

In October 2010, the FDA announced that it would require all bisphosphonate manufacturers to add information regarding the risk of atypical femoral fractures to the Warnings and Precautions section of the drug labels, based on the FDA's conclusion that "these atypical fractures may be related to long-term . . . bisphosphonate use."[54] It reiterated that it

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[51] A 1167.

[52] A 1512.

[53] *Id.*

[54] A 1118. The FDA also announced that it would require a new Limitations of Use statement in the Indications and Usage section of the labels to "describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis." *Id.*

was still "not clear if bisphosphonates are the cause," but noted that "these unusual femur fractures have been predominantly reported in patients taking bisphosphonates."[55] In a conference call accompanying the announcement, the FDA's Deputy Director of the Office of New Drugs stated that the task force report made the FDA "confident" that atypical femur fractures are "potentially more closely related to" long-term use of bisphosphonates "than [the FDA] previously had evidence for."[56]

The same day, the FDA wrote to Merck requesting that Merck add the following language to the Warnings and Precautions section of the Fosamax label:

> Atypical Subtrochanteric and Diaphyseal Femoral Fractures:
>
> Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
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> Atypical femur fractures most commonly occur with minimal or no impact to the affected

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[55] *Id.*

[56] 56 A 1396.

> area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
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> Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out a femur fracture. Subjects presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.[57]

Merck responded by proposing additional language that, according to Merck, was intended to make clear that doctors should attempt to rule out stress fractures. The proposal contained five specific references to "stress fractures." The FDA responded to this proposal by eliminating every instance of the phrase "stress fractures." In rejecting Merck's proposal, the FDA explained that "the term 'stress fracture' was considered and not accepted. The Division believes that for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical

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[57] A 1516-17.

femoral fractures associated with bisphosphonate use."[58] The FDA subsequently approved language nearly identical to its original October 2010 proposal. That language was added to the Fosamax label in January 2011 and has remained there since.

D. Procedural History

After the label change, patients who had taken Fosamax and suffered atypical femur fractures filed lawsuits against Merck throughout the country. In May 2011, the Judicial Panel on Multidistrict Litigation consolidated these cases for pre-trial administration in a multi-district litigation ("MDL") in the District of New Jersey.[59] Since then, the MDL has been assigned to three different district judges[60] and has swelled to over 1,000 cases, each involving a separate patient who allegedly suffered a femur fracture after taking Fosamax.

Although no two complaints in the MDL are identical, all of the actions "share questions of fact arising from similar allegations that use of Fosamax . . . caused femur fractures or similar bone injuries."[61] The individual Plaintiffs in this appeal all allege that they were injured before September 14, 2010, the date the outside expert task force published its report documenting an association between

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[58] A 1540.

[59] *In re: Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 787 F. Supp. 2d 1355 (J.P.M.L. 2011) (hereinafter, "*Fosamax MDL Order*").

[60] The MDL is currently assigned to the Honorable Freda Wolfson.

[61] *Fosamax MDL Order*, 787 F. Supp. 2d at 1356.

bisphosphonate use and atypical femur fractures. According to Plaintiffs,[62] the complaints filed by this cohort generally include a state-law products liability claim for failure to warn, alleging that Fosamax was defective because Merck failed to warn Plaintiffs and their physicians about the risk of atypical femur fractures. Many complaints also claim that Fosamax was defectively designed because the risks of Fosamax exceeded the benefits, or because Fosamax was unreasonably dangerous or more dangerous than an ordinary consumer would expect. Many complaints also include claims for, among other causes of action, negligence, negligent misrepresentation, breach of express and implied warranties, unjust enrichment, punitive damages, and violations of state consumer fraud and deceptive trade practice statutes.[63]

Merck has argued since the inception of the MDL that Plaintiffs' state-law failure-to-warn claims are preempted by FDA regulations. The District Court decided to address preemption after developing a full record in a bellwether trial, the so-called *Glynn* trial. Typical of all plaintiffs in this MDL, the lead plaintiff in *Glynn* claimed that she suffered an atypical femur fracture that was proximately caused by Merck's failure to include adequate fracture warnings on the

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[62] This appeal involves over 500 related cases, and the parties have wisely chosen not to include each complaint in the record. We are therefore necessarily reliant on the parties for information regarding the nature, prevalence and commonality of the plaintiffs' claims.

[63] Although the complaints exclusively plead state-law causes of action, the actions are in federal court on diversity grounds.

Fosamax label.[64] Merck moved for judgment as a matter of law on preemption grounds before and during trial, but the District Court reserved judgment.[65] The jury returned a verdict for Merck on the merits, finding that Ms. Glynn failed to prove by a preponderance of the evidence that she experienced an atypical femur fracture.[66] Despite this verdict, the District Court announced that it would still decide whether the Glynns' claims were preempted.[67]

In June 2013, the District Court issued an opinion concluding that the Glynns' failure-to-warn claim was preempted by federal law. Applying the Supreme Court's decision in *Wyeth*, the court stated that state-law failure-to-warn claims are preempted when "there is 'clear evidence that the FDA would not have approved a change' to the prescription drug's label."[68] The District Court concluded that the Glynns' claim was preempted because the FDA's May 2009 denial of Merck's request to add language about atypical femur fractures to the Warnings and Precautions section of the label was "clear evidence that the FDA would not have approved a label

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[64] Although the *Glynn* plaintiffs brought multiple claims, the only one they actually tried to verdict was a failure-to-warn claim. *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (Glynn v. Merck Sharp & Dohme Corp.)*, 951 F. Supp. 2d 695, 700 & n.5 (D.N.J. 2013) (hereinafter, "*Glynn*").

[65] *Id.* at 700-701.

[66] *Id.* at 701.

[67] *Id.*

[68] *Glynn*, 951 F. Supp. 2d at 702 (quoting *Wyeth*, 555 U.S. at 571).

change to the Precautions section of the label prior to Ms. Glynn's injury."[69]

Shortly after the *Glynn* decision, Merck moved for an order to show cause why all the cases in the MDL alleging injuries prior to the release of the September 2010 task force report should not be dismissed on preemption grounds. Plaintiffs opposed the motion on the ground that resolving their claims through a show-cause procedure would violate their due process right to individual trials. In August 2013, the District Court issued an Order to Show Cause why the pre-September 2010 claims should not be dismissed on preemption grounds, and the parties submitted briefing. Although both sides disputed the propriety of the show-cause procedure and the substance of Merck's preemption arguments, the parties and the District Court all agreed that Federal Rule of Civil Procedure 56 "provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s)."[70]

After briefing, the District Court granted summary judgment to Merck and ruled that all claims made by plaintiffs who were injured prior to September 14, 2010 were preempted under *Wyeth*. Specifically, the court ruled that: (1) Merck had met its initial burden

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[69] *Id.* at 703.

[70] *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, MDL No. 2243, Master Dkt. No. 08-08 (JAP)(LHG), 2014 WL 1266994, at *8 (D.N.J. Mar. 26, 2014) (hereinafter, "*Summary Judgment Order*"). The parties continue to agree that Rule 56 is the proper framework to apply, although they dispute how to apportion the parties' burdens of production and persuasion.

of demonstrating that there was no genuine issue of material fact as to preemption in *Glynn*, and that Plaintiffs therefore bore the burden of producing a genuine issue for trial; (2) Plaintiffs had failed to create a genuine issue as to preemption; (3) it was proper to use a show-cause proceeding to apply the *Glynn* preemption ruling to other MDL cases; (4) Plaintiffs' design-defect and other non-warning claims were also preempted because they sounded in failure to warn; and (5) Plaintiffs' alternate theories that Merck should have added information about fractures to the Adverse Reactions section of the label prior to 2009 and should have warned that Fosamax's long-term benefits were limited should be dismissed.

With respect to the failure-to-warn claims, the District Court reiterated its conclusion from *Glynn* that "the fact that the FDA never required [Merck] to submit new language or change the label demonstrates that the FDA did not think that the label should have been changed at that time."[71] This evidence "remain[ed] unchanged" and provided "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning."[72] As to the non-failure-to-warn claims (including claims for design defect, negligence, fraud, breach of warranty, deceptive trade practice, and unjust enrichment), the District Court concluded that that these claims "are based entirely on the premise that Fosamax had

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[71] *Id.* at *16 (quoting *Glynn*, 951 F. Supp. 2d at 703-04) (alterations omitted).

[72] *Id.*

risks which should have been disclosed to consumers" and therefore "ultimately hinge[ ] on the adequacy of Fosamax's warning."[73] Because these claims "rise and fall with a claim for failure to warn," they too were preempted.[74] This appeal followed.[75]

II. LEGAL BACKGROUND

The primary issue in this case is whether Plaintiffs' state-law failure-to-warn claims are preempted by federal law under the Supreme Court's decision in *Wyeth*. This is not a straightforward determination. *Wyeth* says only that a claim is preempted when there is "clear evidence" that the FDA would not have approved a label change. This standard is cryptic and open-ended, and lower courts have struggled to make it readily administrable. This appeal, however, requires us to do so. To assess whether Merck is entitled to summary judgment on

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[73] *Id.* at *12, *14.

[74] *Id.* at *12, *14.

[75] This appeal involves only those Plaintiffs who alleged that they were injured before September 14, 2010. *See, e.g., id.* at *17 (granting summary judgment to Merck on "all claims made by the Plaintiffs . . . with injuries that occurred prior to September 14, 2010"). Plaintiffs inform us that there are "approximately 570 remaining cases in the MDL involving plaintiffs who were injured after September 14, 2010." Pls. Br. 8; *see also* A 2067-80. In June 2015, the District Court conditionally dismissed these remaining actions without prejudice, concluding that they "are based on the alleged inadequacy of the pre-2011 Fosamax label" and that our decision here would "determine whether the claims of the remaining Plaintiffs in this litigation . . . remain viable or not." A 2065. We express no view regarding the effect of today's ruling on the remaining plaintiffs' claims.

its affirmative preemption defense, we must answer two questions: What is "clear evidence"? And who should determine whether clear evidence exists?

For the following reasons, we conclude that (1) the term "clear evidence" refers solely to the applicable standard of proof, and (2) the ultimate question of whether the FDA would have rejected a label change is a question of fact for the jury rather than for the court. By describing the ultimate question as one of fact for the jury, we do not mean to suggest that summary judgment is categorically unavailable to a manufacturer asserting a preemption defense. When there is no genuine issue of material fact—that is, when no reasonable jury applying the clear-evidence standard of proof could conclude that the FDA would have approved a label change— the manufacturer will be entitled to judgment as a matter of law. We simply hold that, at the summary judgment stage, the court cannot decide for itself whether the FDA would have rejected a change, but must instead ask whether a reasonable jury could find that the FDA would have approved the change.

A. Federal Preemption Doctrine: Impossibility Preemption and the Supreme Court's Decision in *Wyeth v. Levine*

i. Impossibility Preemption

The Supremacy Clause establishes that federal law "shall be the supreme Law of the Land."[76] The Supremacy Clause, therefore, preempts "state laws

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[76] U.S. Const., Art. VI, cl. 2.

that 'interfere with, or are contrary to,' federal law."[77] There are several varieties of preemption; the one at issue here is called "conflict" or "impossibility" preemption. Impossibility preemption applies, and state law must give way, when "it is 'impossible for a private party to comply with both state and federal requirements.'"[78] "The question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."[79]

In this case, Plaintiffs claim that state law obligated Merck to add a warning about atypical femur fractures to the Fosamax label. At issue is whether federal law—here, FDA regulations—prevented Merck from adding the type of warnings that Plaintiffs claim were required under state law. The Supreme Court confronted a similar question in *Wyeth*, and its opinion governs our analysis here.

ii. The *Wyeth* Decision

In *Wyeth*, the Supreme Court addressed whether and to what extent state-law failure-to-warn claims are preempted by the FDCA and federal drug-labeling regulations. The Court held that failure-to-warn claims against drug manufacturers generally are not preempted by FDA approval of the drug's warning label. But such a claim *is* preempted by federal law when there is "clear evidence" that the

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[77] *Hillsborough Cty., Florida v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712 (1985) (quoting *Gibbons v. Ogden*, 22 U.S. 1, 211 (1824)).

[78] *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618 (2011) (quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287 (1995)).

[79] *Id.* at 620.

FDA would not have approved the warning that a plaintiff claims was necessary.

The plaintiff in *Wyeth* developed gangrene when a physician's assistant injected her with the antinausea drug Phenergan. She brought a state-law failure-to-warn claim against *Wyeth*, the manufacturer of Phenergan, for failing to provide an adequate warning about the risks involved with various methods of administering the drug. A jury concluded that the plaintiff's injury was caused by *Wyeth*'s inadequate warning label. *Wyeth* argued on appeal that the state-law failure-to-warn claims were preempted because it was impossible to comply with both state-law warning duties and federal labeling obligations.[80]

The Supreme Court rejected *Wyeth*'s argument. It began by citing the "central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."[81] Under this rule, a manufacturer "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[82] Thus, when the risks of a particular drug use become apparent, the manufacturer has "a duty to provide a warning that adequately describe[s] that risk."[83]

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[80] *Wyeth*, 555 U.S. at 559-64.

[81] *Id.* at 570-71.

[82] *Id.* at 571.

[83] *Id.*

In response to Wyeth's contention that federal law made it impossible to add the warnings the plaintiff claimed were necessary, the Court observed that drug manufacturers are allowed to strengthen an FDA-approved warning label without FDA approval through the CBE process.[84] Wyeth therefore could not establish impossibility preemption because the CBE regulation "permitted [Wyeth] to provide . . . a warning [of the risk of gangrene] before receiving the FDA's approval."[85]

The Supreme Court cautioned, however, that the mere availability of a CBE label amendment would not always defeat a manufacturer's preemption defense, because the FDA "retains authority to reject labeling changes."[86] Thus, where there is "clear evidence that the FDA would not have approved a change" to the label, federal law preempts state-law claims premised on the manufacturer's failure to make that change.[87] Impossibility preemption applies in that instance because the manufacturer would be legally prevented by the FDA from taking the very action that state law ostensibly requires.[88]

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[84] *Id.* at 568.

[85] *Id.* at 571.

[86] *Id.*

[87] *Id.*

[88] If a manufacturer retains a warning that the FDA has rejected, the drug may be deemed "misbranded" in violation of federal law. *See* 21 U.S.C. § 352(a) (drug shall be considered misbranded "[i]f its labeling is false or misleading in any particular"); A 1501 (FDA letter rejecting Merck's PAS proposal to amend the Fosamax label and stating that "[t]hese products

The manufacturer in *Wyeth* could not take advantage of the clear-evidence exception because it had "offered no such evidence" that the FDA would have rejected the warning sought by the plaintiff.[89] But the Supreme Court made it clear that if a manufacturer does present "clear evidence" that the FDA would reject a plaintiff's proposed warning, it would have a complete preemption defense to any state-law failure-to-warn claims.

In this case, Merck claims that the FDA's 2009 rejection of its proposed label amendment is just such "clear evidence."

B. Defining "Clear Evidence"

Courts applying the *Wyeth* preemption rule confront an immediate question: what is "clear evidence that the FDA would not have approved a change"? The *Wyeth* Court did not define the "clear evidence" standard or explain how courts should apply it. The only guidance the Court offered was to call impossibility preemption a "demanding defense."[90] In the absence of explicit direction or a coherent doctrinal framework, lower courts have been understandably reluctant to articulate firm definitions of the standard or its requirements. For example, several of our sister circuits have decided preemption cases by simply treating the facts of

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may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change before approval of these supplemental applications").

[89] *Wyeth*, 555 U.S. at 571-72.

[90] *Id.* at 573.

Wyeth as a yardstick: if the evidence for FDA rejection in a given case is less compelling than the manufacturer's evidence in *Wyeth*, the thinking goes, then there is clear evidence that the FDA would not have approved a label change and the manufacturer's preemption defense fails.[91] Many district courts have adopted a similar, if more complex. approach of exhaustively surveying the post-*Wyeth* case law and then testing the facts of a particular case against prior decisions.[92] Both approaches produce valid outcomes in individual cases, but neither clarifies or builds out the doctrine. The result is an anomaly in our preemption jurisprudence: the number of cases applying the clear evidence standard continues to

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[91] *See Mason v. Smithkline Beecham Corp.*, 596 F.3d 387, 392-96 (7th Cir. 2010) (stating that *Wyeth* provides an "intellectual anchor" because "if the evidence here is less compelling than it was in [*Wyeth*], we will not find preemption," and holding that preemption was unwarranted because the manufacturer's evidence was not "any more compelling"): *Gaeta v. Perrigo Pharms. Co.*, 630 F.3d 1225, 1235-37 (9th Cir. 2011) (observing that "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard" and holding that preemption was unwarranted "[b]ecause the evidence presented by Perrigo in this case is no more compelling than the evidence considered and rejected by the Supreme Court in [*Wyeth*]" (abrogated on other grounds, *PLIVA*, 564 U.S. 604).

[92] *See, e.g., In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108 (S.D. Cal. 2015); *Seufert v. Merck Sharp & Dohme Corp.*, No. 13-cv-2169 AJB (MDD), 2016 WL 3369512 (S.D. Cal. May 11, 2016).

grow, yet "the clear evidence standard remains undefined."[93]

Today, we hold that the Supreme Court intended to announce a standard of proof when it used the term "clear evidence" in *Wyeth*.

The *Wyeth* Court articulated the "clear evidence" exception as follows: "[A]bsent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for *Wyeth* to comply with both federal and state requirements."[94] This formula has three components: (1) a legal rule that defines the circumstances in which a manufacturer is absolved of state-law liability (it must be impossible for the manufacturer to comply with both federal and state requirements); (2) a factual showing that satisfies the legal rule (the FDA would not have approved the proposed label change); and (3) a standard of proof that specifies how convincing the factual showing must be (the manufacturer must show that the FDA would not have approved the proposed label change by "clear evidence"). The term "clear evidence" therefore does not refer directly to the *type* of facts that a manufacturer must show, or to the circumstances in which preemption will be appropriate. Rather, it specifies how *difficult* it will be for the manufacturer to convince the factfinder that the FDA would have rejected a proposed label change. The manufacturer must prove that the FDA

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[93] *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1119.

[94] 555 U.S. at 571.

would have rejected a warning not simply by a preponderance of the evidence, as in most civil cases, but by "clear evidence."

Our conclusion that the *Wyeth* Court intended the term "clear evidence" to denote a standard of proof is supported by the Supreme Court's prior usage of the term. For example, the Court has consistently held that a complainant alleging official government misconduct must present "clear evidence" of unlawful behavior.[95] "Clear evidence" in this context is understood to be a standard of proof, rather than a condition on the type of facts that must be proven.[96] Similar examples are found in the bankruptcy and patent settings.[97]

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[95] *See, e.g., United States v. Chemical Found., Inc.*, 272 U.S. 1, 14-15 (1926) ("The presumption of regularity supports the official acts of public officers, and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties."); *United States v. Armstrong*, 517 U.S. 456, 465 (1996) (criminal defendant alleging racially discriminatory prosecution must present "clear evidence" that prosecutorial policy had discriminatory effect and purpose); *Reno v. American-Arab Anti-Discrimination Comm.*, 525 U.S. 471, 489 (1999) (selective prosecution claim requires "clear evidence" of unlawful action).

[96] *See Reno*, 525 U.S. at 489 (stating that clear evidence is "the standard for proving" a selective prosecution claim); *United States v. Jarrett*, 447 F.3d 520, 525 (7th Cir. 2006) (describing clear evidence as "[t]he standard of proof" for selective prosecution claims).

[97] *See Oriel v. Russell*, 278 U.S. 358, 362-63 (1929) (when a party seeks turnover in a bankruptcy proceeding, "[a] mere preponderance of evidence . . . is not enough" and the court deciding the motion "should therefore require clear evidence"); *Microsoft v. i4i Ltd. P'ship*, 564 U.S. 91, 97, 11314 (2011)

Nor must we look far to discern the meaning of "clear evidence," as Supreme Court usage confirms that the term is synonymous with "clear and convincing evidence."[98] The latter is a well-recognized intermediate standard of proof—more demanding than preponderance of the evidence, but less demanding than proof beyond a reasonable doubt. Black's Law Dictionary defines clear and convincing evidence as "evidence indicating that the thing to be proved is highly probable or reasonably certain."[99] We adopt that definition here. It is consistent with both settled understanding and *Wyeth*'s instruction that the clear-evidence test is a "demanding defense" meant to represent a longstanding "presumption against pre-emption."[100]

We therefore conclude that for a defendant to establish a preemption defense under *Wyeth*, the factfinder must conclude that it is highly probable that the FDA would not have approved a change to the drug's label.

(Federal Circuit's interpretation of Patent Act as requiring "clear evidence" of invalidity accurately stated the statutory standard of proof).

[98] *See Microsoft*, 564 U.S. at 97, 113-14 (equating Federal Circuit's "clear evidence" standard with "clear and convincing" standard); *Oriel*, 278 U.S. at 362-63 (equating "clear evidence" with "clear and convincing evidence"); *accord Ramsey v. United Mine Workers of Am.*, 401 U.S. 302, 307-09, 311 (1971) (interpreting statute requiring "clear proof" as requiring "clear and convincing evidence").

[99] Black's Law Dictionary 674 (10th ed. 2009).

[100] *Wyeth*, 555 U.S. at 571-73, 565 n.3.

C. Whether the FDA Would Have Rejected a Label Change is a Question of Fact for the Jury

Once "clear evidence" is understood as a standard of proof rather than a condition on the type of facts to be proven, the *Wyeth* test narrows to a single inquiry: would the FDA have approved the label change that Plaintiffs argue was required?

Oral argument in this case revealed a fundamental yet unexplored disagreement between the parties. Merck claimed that the *Wyeth* preemption test presents a pure question of law that must be decided by a court, not a jury. Plaintiffs argued that *Wyeth* preemption poses a mixed question of fact and law that may require jury factfinding in appropriate circumstances. The distinction is crucial in this case because it dictates the course of our summary judgment analysis. If the question of whether the FDA would have rejected Plaintiffs' proposed warning is a question of law for the court, then we may simply answer it ourselves; but if it is a question of fact for the jury, then we must instead attempt to anticipate the range of answers that could be given by reasonable jurors applying the clear evidence standard and then determine whether summary judgment is appropriate. Having reviewed the case law and the parties' supplemental briefing on the issue, we conclude that the question of whether the FDA would have rejected a proposed label change is a question of fact that must be answered by a jury.[101]

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[101] Our discussion of the allocation of decision-making authority, both here and elsewhere in this Opinion, applies in

The court's role at the summary judgment stage is therefore limited to determining whether there are genuine issues of material fact that preclude judgment as a matter of law.

i. Conflict Preemption Can Require Fact Determinations by a Jury

Merck makes two general, threshold arguments in favor of treating *Wyeth* preemption as a purely legal question to be answered by the court.

First, Merck notes that the vast majority of courts applying *Wyeth* have assumed, either explicitly or implicitly, that *Wyeth* preemption presents a question of law. This observation is only somewhat accurate and wholly unpersuasive.

Wyeth does not indicate whether the "clear evidence" test poses a legal or factual question. Nor is it possible to divine a clear answer from the Supreme Court's application of the test in *Wyeth* itself.[102] However, the Supreme Court did decide

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cases tried to a jury. In a bench trial, of course, judicial factfinding will be both appropriate and necessary.

[102] Had *Wyeth* come up on appeal from a grant of summary judgment, for example, the Court would have been forced to address whether the question of what the FDA would have done should be answered by a court or by a jury. But *Wyeth* was an appeal of a post-trial motion for judgment, following a full jury trial and post-verdict proceedings in which the trial court made explicit fact findings, based on the trial record, directed at the preemption issue. *Wyeth*, 555 U.S. at 561-63. The Supreme Court concluded on the basis of that complete record that there was "no . . . evidence" that the FDA would have rejected a warning. *Id.* at 572. The combination of (1) a complete fact record that (2) contained zero evidence to support preemption

that the evidence presented in *Wyeth* was not sufficient to pass the clear evidence test. Therefore, in light of the Court's definitive holding that the evidence in *Wyeth* did not pass muster, the many federal courts that have applied the *Wyeth* preemption test have simply compared the evidence presented in their cases to the evidence presented in *Wyeth*. For example, in *Mason v. Smithkline Beecham Corp.*, the Seventh Circuit walked through the record evidence and concluded that, "in light of the extensive showing required by [*Wyeth*]," the manufacturer "did not meet its burden of demonstrating by clear evidence that the FDA would have rejected a label change."[103] The Ninth Circuit took a similar approach in *Gaeta v. Perrigo Pharmaceuticals Co.*, and explicitly stated that since "the only guidance this court has is that the evidence presented in [*Wyeth*] was insufficient to meet the clear evidence standard," the manufacturer would not meet the clear evidence standard if the "evidence in this case [is] less compelling than [that] in [*Wyeth*]."[104] Many other circuits have followed this approach and have found no preemption because the

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eliminated the need for remand, and thereby obviated the need to explain which judicial actor should make preemption-related findings in the first instance. And since the complete record contained no evidence whatsoever indicating that the FDA would not have approved a label change, the Supreme Court had no reason to consider whether a jury could have reached a contrary conclusion.

[103] *Mason*, 596 F.3d at 393-96.

[104] *Gaeta*, 630 F.3d at 1235-36.

evidence in those cases fell short of the record in *Wyeth*.[105]

It is possible to characterize this approach as a tacit acknowledgment that the "clear evidence" test is a legal question to be answered directly by the court. *Mason*, for example, was an appeal of a grant of summary judgment, but the court did not engage in a Rule 56 disputed-facts analysis or consider whether a reasonable jury could reach a contrary conclusion. At the same time the court also did not explain why the *Wyeth* test should be resolved by the court in the first instance. We do not lightly discount the wisdom of our sister circuits and the district courts that have grappled with these issues. But there is a difference between rejecting another court's considered judgment, on the one hand, and taking up an issue that has not been thoroughly analyzed, on the other. Furthermore, the approach taken by our sister circuits would be entirely consistent with our decision that the "clear evidence" test is a fact question that is ultimately for a jury to decide. After all, by comparing the evidence presented in these cases with

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[105] *See, e.g.*, *Demahy v. Actavis, Inc.*, 593 F.3d 428, 446 (5th Cir. 2010) ("The record here contains nothing, let alone 'clear evidence,' that suggests the FDA would have rejected a labeling proposal from Actavis."); *Mensing v. Wyeth, Inc.*, 588 F.3d 603, 610-11 (8th Cir. 2009) ("The record contains nothing, let alone 'clear evidence,' to suggest the FDA would have rejected a labeling proposal from any of them."); *but see Miller v. Smithkline Beecham Corp.*, 381 F. App'x 776 (10th Cir. 2010) (unpublished) (without any prior discussion, remanding "to give the [district] court the opportunity to make evidentiary findings and analyze the record in light of [*Wyeth's*] new 'clear evidence' standard").

the evidence presented in *Wyeth*, these circuits are in fact engaging in a summary judgment analysis, even if they do not name it.

Second, Merck asserts that conflict preemption *always* presents a pure question of law. To be sure, we have made numerous offhand statements that seem to support Merck's position.[106] And as Merck points out, several district courts relying on similar language have concluded, albeit without substantial analysis, that a manufacturer's entitlement to the *Wyeth* preemption defense is a question of law for the court rather than the jury.[107]

The "rule" Merck cites, however, is one of thumb rather than law. It is true that *most* preemption cases present purely legal questions—for example, whether Congress intended to preempt state law, how to interpret the scope of an express preemption provision, or whether two regulatory schemes are facially incompatible. But it is equally clear that preemption can be, and sometimes must be, a fact question for the jury.

The Supreme Court's opinion in *Boyle v. United Technologies Corp.*[108] illustrates the distinction. In

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[106] *See, e.g., In re Federal-Mogul Global Inc.*, 684 F.3d 355, 364 n.16 (3d Cir. 2012) ("The scope of preemption presents a pure question of law, which we review *de novo*."); *Horn v. Thoratec Corp.*, 376 F.3d 163, 166 (3d Cir. 2004) ("This Court also exercises plenary review over a district court's preemption determination, as it is a question of law.").

[107] *See Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1267 (W.D. Okla. 2011); *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1114.

[108] 487 U.S. 500 (1988).

Boyle, as in *Wyeth*, the Supreme Court defined the scope of conflict preemption in a particular setting and announced the factual showing that a defendant must make to prove the affirmative preemption defense. Specifically, the Court held that "[l]iability for design defects in military equipment cannot be imposed, pursuant to state law, when (1) the United States approved reasonably precise specifications; (2) the equipment conformed to those specifications; and (3) the supplier warned the United States about the dangers in the use of the equipment that were known to the supplier but not to the United States."[109] The Court clarified that "whether the facts establish the conditions for the defense is a question for the jury."[110] The proper question on summary judgment, therefore, was whether a "reasonable jury could, under the properly formulated defense, have found for the petitioner on the facts presented."[111] It would be error, the Court said, for a court to "assess[ ] on its own whether the defense had been established."[112]

While our court has not gone so far as to declare that any one species of preemption defense categorically requires jury factfinding, we have acknowledged that the availability of the defense can turn on questions of fact. In *MD Mall Associates, LLC v. CSX Transportation, Inc.*,[113] we determined

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[109] *Id.* at 512.

[110] *Id.* at 514.

[111] *Id.*

[112] *Id.*

[113] 715 F.3d 479 (3d Cir. 2013).

that the question of whether state-law storm water trespass claims conflicted with federal railroad-safety regulations had to be addressed "under the circumstances of this particular case."[114] We therefore held that whether the defendant railroad could reasonably comply with federal drainage requirements while also complying with Pennsylvania law regarding storm water trespass "is a question of fact."[115] Having so concluded, we remanded for further development of the factual record.

Boyle and *MD Mall* confirm that the availability of a conflict preemption defense is not automatically a question of law that must be kept from the jury. The question, therefore, is whether there are independent jurisprudential or practical reasons to conclude that *Wyeth* preemption, specifically, requires a legal or a factual determination.

ii. Whether the FDA Would Have Approved a Label Change is a Factual Question Appropriate for the Jury

There are no general, hard-and-fast rules that we can use to distinguish fact questions from legal ones.[116] The Supreme Court has candidly acknowledged that "the appropriate methodology for

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[114] *Id.* at 496 (alteration omitted) (quoting *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 373 (2000)).

[115] *Id.*

[116] *See Pullman-Standard v. Swint*, 456 U.S. 273, 288 (1982) (the Supreme Court has not devised a "rule or principle that will unerringly distinguish a factual finding from a legal conclusion").

distinguishing questions of fact from questions of law has been, to say the least, elusive."[117] In the absence of a governing principle, we look to the fact/law distinctions drawn by our court in similar cases, practical considerations regarding the allocation of decision-making authority between judge and jury, and the text of *Wyeth* itself. What we discern from these sources is that the question at the heart of the *Wyeth* test—would the FDA have approved the label change plaintiffs argue was required?—is little different from the type of fact questions that are routinely given to a jury.

At root, *Wyeth* requires the decisionmaker to use an existing fact record to predict the outcome of a hypothetical scenario. The question posed to the decisionmaker in this case is: based on the contemporaneous medical literature and the interactions between Merck and the FDA that actually *did* happen, what *would* have happened if Merck had proposed the warning plaintiffs say was required? We think this question is one of fact, for three reasons.

First, we have recognized that an assessment of the probability of a future event should generally be categorized as a finding of fact, even if that finding automatically generates a legal consequence. In *Kaplun v. Attorney General of the United States*,[118] we held that a determination of the probability of future torture was a fact question subject to clear-error review. In so doing, we observed in general

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[117] *Miller v. Fenton*, 474 U.S. 104, 113 (1985).

[118] 602 F.3d 260, 269 (3d Cir. 2010).

terms that "[a] present probability of a future event is something distinct from its legal effect that is made up of facts and actually exists but is not a tangible thing, or actual occurrence."[119] Even though the future event has not occurred, and even if the prediction as to that event's likelihood is dispositive of a legal issue, "the likelihood itself remains a factual finding that can be made *ex ante* the actual outcome."[120] The *Kaplun* panel cited a number of other nonimmigration cases in which we or other circuits have held that inferences drawn from historical facts concerning the likelihood of future events are findings of fact, not law.[121] Here, the corresponding conclusion is that the task of assessing the probability that the FDA would have rejected a particular warning is a factual inquiry rather than a legal one.[122]

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[119] *Id.* at 269 (alterations and internal quotations omitted).

[120] *Id.* at 269-70. In other words, the likelihood of an event occurring "is what a decision-maker in an adjudicatory system decides now as part of a factual framework for determining legal effect." *Id.* at 269.

[121] *See United States v. Stewart*, 452 F.3d 266, 273 (3d Cir. 2006) (whether the release of an individual creates a substantial risk of future danger to society is a finding of fact); *Martin v. Cooper Elec. Supply Co.*, 940 F.2d 896, 900 (3d Cir. 1991) (inferences from historical facts are factual findings reviewed for clear error); *Onishea v. Hopper*, 171 F.3d 1289, 1300-01 (11th Cir. 1999) (en banc) (district court's finding as to the risk of future prison violence based on conflicting evidence was a factual determination reviewed for clear error).

[122] We recognize that the *Wyeth* test is something of an oddity. In a typical case, the historical facts are in dispute and the jury is tasked with figuring out what actually happened. In the case

Second, *Wyeth* requires the decisionmaker to weigh conflicting evidence and draw inferences from the facts—tasks that the Supreme Court tells us "are jury functions, not those of a judge."[123]

The present case is illustrative. Plaintiffs, for their part, rely heavily on the May 2009 letter from Dr. Scott Monroe of the FDA rejecting Merck's proposed warning. According to Plaintiffs, the text of this letter demonstrates that the FDA (or at least Dr. Monroe) objected only to the allegedly misleading term "stress fractures," and does not establish that the FDA was unconvinced of the link between bisphosphonate use and atypical femur fractures. Merck, meanwhile, directs our attention away from Dr. Monroe's letter and instead toward a series of informal FDA communications from the same time period between Dr. Monroe and Merck, which they claim demonstrate that the FDA (or at least Dr. Monroe) was unconvinced of a scientifically-proven link between bisphosphonates and atypical fractures.[124] In short: both sides ask us to (1) draw competing inferences from separate pieces of record

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before us, the historical facts are largely undisputed, and the primary disputed fact is the ultimate fact of what *would* have happened. This fact is in turn wholly determinative of the legal question. The law is clear, however, that "an issue does not lose its factual character merely because its resolution is dispositive of the ultimate constitutional question." *Miller*, 474 U.S. at 113. That is the same basic conclusion we reached in *Kaplun*: just because a fact finding completely resolves a legal issue does not alter its fundamentally "factual" character.

[123] *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

[124] *See* A 1498, 1971.

evidence and (2) weigh those inferences against one another. These are tasks reserved for jurors, not judges.

Third, the task of predicting the FDA's likely actions requires multiple assessments of FDA officials' motives and thought processes. Consider, for example, some of the questions that must be answered to arrive at a determination of whether the FDA would have rejected Plaintiffs' warning. How convinced or skeptical were FDA officials of the link between bisphosphonates and atypical femur fractures? Even if FDA officials were unconvinced of a firm link, might they nonetheless have agreed that there was "reasonable evidence of a causal association," as the CBE regulation requires? Did the FDA reject Merck's 2009 proposal because it was unconvinced by the science or because it disliked the stress-fracture language? What, if anything, can we infer from Dr. Monroe's contemporaneous oral statement that the "conflicting nature of the literature" concerning a possible fracture link "does not provide a clear path forward"? Whatever the FDA's position might have been on the association between bisphosphonates and atypical femur fractures, was that position an accurate predictor of its likely response to a proposed warning? In other words, how confidently can we extrapolate FDA officials' hypothetical reactions from their previous statements and actions?

These are all, essentially, inquiries about motive or state of mind: what were FDA officials thinking, and how would that disposition have conditioned their response to plaintiffs' hypothetical proposed warning? And questions of motive, intent, and state

of mind are typically understood to be fact questions committed to the jury rather than the court.[125]

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[125] *See Pullman-Standard*, 456 U.S. at 288 ("Treating issues of intent as factual matters for the trier of fact is commonplace."); *Monteiro v. City of Elizabeth*, 436 F.3d 397, 405 (3d Cir. 2006) ("Motive is a question of fact that must be decided by the jury"); *Grant v. City of Pittsburgh*, 98 F.3d 116, 125 (3d Cir. 1996) ("[T]he issue of state of mind will always be a question of fact").

One might object that the FDA acts as a body rather than through individuals, thereby rendering questions of "motive" and "intent" irrelevant in this setting. The key evidence in this case belies that assumption. At oral argument, Merck's counsel stated that the single best piece of evidence that the FDA would have rejected a revised warning is a set of notes, prepared by a Merck employee, recounting a telephone conversation with Dr. Monroe of the FDA—the same official who wrote the May 2009 letter formally rejecting Merck's proposed additions to the Warnings and Precautions section. According to the employee's notes, Dr. Monroe said that Merck's "elevation of this issue to a precaution in the labeling" was prolonging review, that the "FDA would like to approach the issue of a precaution from the [perspective] of all bisphosphonates," and that because the "conflicting nature of the literature does not provide a clear path forward, . . . more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a precaution around these data." A 1971.

To gauge the import of these statements, a decisionmaker would need to, at a minimum, (1) make a credibility determination regarding the Merck employee who drafted the notes; (2) determine the veracity and accuracy of the notes; (3) determine the semantic meaning of Dr. Monroe's statements; (4) infer Dr. Monroe's intent and state of mind when making the statements; and (5) weigh that inference against whatever competing inferences can be drawn from Dr. Monroe's subsequent letter rejecting Merck's proposed warning. These are precisely the types of personal evaluations and weight-of-the-evidence assessments that we commit to jurors in the first instance.

As a fallback position, Merck argues that even if the *Wyeth* inquiry is factual in nature, it should be committed to the court rather than the jury for reasons of institutional competence.[126] Merck relies heavily on *Markman v. Westview Instruments, Inc.*,[127] in which the Supreme Court held that "construction of a patent, including terms of art within its claim, is exclusively within the province of the court."[128] The *Markman* Court based this conclusion, in part, on the general rule that "[t]he construction of written instruments is one of those things that judges often do and are likely to do better than jurors."[129] Here, the question of how the FDA would have responded to a proposed warning is informed by the regulations

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We acknowledge, of course, that the *Wyeth* inquiry may sometimes require the factfinder to impute motive or intent to the FDA as a whole. But as the Supreme Court has recognized, the difficulty of assessing collective intent is not a reason to treat the assessment as something other than a factual inquiry. For example, the Court has held that the question of whether a corporation harbored discriminatory intent is a question of fact. *Pullman-Standard*, 456 U.S. at 289 ("[D]iscriminatory intent . . . is not a question of law and not a mixed question of law and fact."). Here too, the questions of why the FDA took certain actions or what can be inferred from its pronouncements are questions of fact for a jury.

[126] *See Miller*, 474 U.S. at 114 ("[T]he fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question.").

[127] 517 U.S. 370 (1996).

[128] *Id.* at 372.

[129] *Id.* at 388.

that constrain FDA action—in this case, the CBE regulation. That regulation permits the FDA to add an adverse reaction in the Warnings and Precautions section "as soon as there is reasonable evidence of a causal association with a drug."[130] Agency guidance clarifies that "reasonable evidence" is "a standard that could be met by a wide range of evidence," including evidence that "would not also support a higher evidentiary standard, such as a finding that there is a 'preponderance' of evidence that a product actually causes a particular kind of adverse event."[131] Merck therefore claims that application of the clear evidence standard should be left to the courts because it "calls for the interpretation of regulations and agency records freighted with legal meaning."[132]

This argument misapprehends the nature of the factfinder's task under *Wyeth*. That task is to predict how the FDA would have reacted in a hypothetical scenario. The jury therefore is not being asked to supply a plenary construction of the CBE regulation (or any other written instrument) in the first instance. It is instead being asked to *apply* the requirements of that regulation to the facts, in aid of a prediction as to the FDA's behavior.

The operative language in the CBE regulation is neither uncommon nor abstruse. The "reasonable evidence of a causal association" standard requires law-to-fact applications of the sort that courts routinely give to juries in tort cases. It combines two

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[130] 21 C.F.R. § 201.57(c)(6)(i).

[131] 73 Fed. Reg. 49,603, 49,604 (Aug. 22, 2008).

[132] Merck Supp. Ltr. Br. 4.

classic jury questions: (1) whether a causal link between two events is too attenuated, and (2) whether the evidence meets a certain proof threshold. These determinations are well within the province of a properly instructed jury, and we do not think that their inclusion in the larger *Wyeth* inquiry merits reallocation of the factfinding function.

Plaintiffs, meanwhile, argue that judicial decision-making is required when a preemption determination "depends on construction of final, written regulatory actions by the FDA."[133] They further claim that the FDA's May 2009 response letter is just such a "final" document, and urge us to construe it "as a matter of law."[134] We will not go so far. As noted above, it is true that courts are typically charged with determining the construction (*i.e.*, the legal effect) of a writing, as opposed to its interpretation (*i.e.*, the semantic meaning of specific terms). But that general rule has little bearing on the disposition of this case. The question for preemption purposes is whether the FDA would have approved a different label amendment than the one it actually rejected in the May 2009 letter. The factfinder therefore must parse the FDA's May 2009 letter not to determine its legal effect in the first instance, but rather to discern what it suggests about the FDA's likely response to a differently worded proposal. This too is an appropriate task for the jury.[135]

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[133] Pls. Supp. Ltr. Br. 3.

[134] *Id.* 4.

[135] We do not opine on Plaintiffs' contention that the May 2009 letter rejecting Merck's PAS application was a "final regulatory

action." If in future cases a court is confronted with a formal regulatory pronouncement that has the force or effect of law, it may be necessary for the court to determine the scope of its legal effect before submitting the ultimate fact question to the jury. A request for such a ruling could be made by motion in limine or at summary judgment. But that exercise is unnecessary here because the immediate "legal" effect of the May 2009 letter, if any, was simply to reject Merck's proposed warning. That limited determination informs but does not answer the larger question of whether the FDA would have approved a differently-worded warning.

Pivoting to the merits, Plaintiffs direct our attention to an FDA regulation stating that an FDA response letter must "describe all of the specific deficiencies that the agency has identified" in an application. 21 C.F.R. § 314.110(a). Plaintiffs claim that since the May 2009 FDA response letter did not mention any concern over the scientific evidence of a causal association between Fosamax and fractures, we can determine as a matter of law that the FDA would have accepted a proposal that eliminated reference to stress fractures. This is a step too far. Again, the question for the factfinder is whether the FDA would have approved a different warning from the one it rejected. The combination of § 314.110's "complete description" requirement and the FDA's silence in the May 2009 response letter could certainly permit an inference about the FDA's contemporaneous thinking, and thereby an additional inference about how the FDA would have responded to a different warning. But it does not, and cannot, prove *as a matter of law* that the FDA would have accepted a warning of the type proposed by Plaintiffs.

Nor, for that matter, are we ready to blindly accept Plaintiffs' implicit assumption that Dr. Monroe, the author of the May 2009 letter, followed § 314.110 to a T or had its requirements foremost in mind when drafting. After all, Merck's contention is that Dr. Monroe gave additional reasons for the rejection, not disclosed in the May 2009 letter, in his telephone communications with Merck. We of course do not mean to impugn Dr. Monroe or to suggest that the May 2009 letter did not in fact comply with § 314.110. But the facts of this case

Accordingly, we do not see any convincing prudential reasons to commit the *Wyeth* inquiry to a court rather than a jury. The basic question that *Wyeth* poses to a factfinder—in a counterfactual setting, what do you think the FDA would have done?—requires an evaluative inference about human behavior based on correspondence, agency statements, contemporaneous medical literature, the requirements of the CBE regulation, and whatever intuitions the factfinder may have about administrative inertia and agency decision-making processes. This assessment is certainly complex, but it does not require any special legal competence or training.

We therefore conclude that the question of whether the FDA would have approved a plaintiff's proposed warning is a question of fact for the jury. A state-law failure-to-warn claim will only be preempted if a jury concludes it is highly probable that the FDA would not have approved a label change.

This decision would change how the preemption defense is presented and utilized in only a subset of cases. As before, drug manufacturers are free to raise a preemption defense, and either party may move for summary judgment on this issue after discovery. Upon summary judgment, district courts will compare the evidence presented with the evidence in *Wyeth*, to determine whether it is more or less compelling. This is in effect what the other

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demonstrate that we cannot presume the existence of undisputed facts based solely on anticipated compliance with a regulatory rule.

circuits have done. A trial by jury would only be necessary in those cases where the evidence presented is more compelling than that in *Wyeth* but no "smoking gun" rejection letter from the FDA is available. And this need not be at a great expense to either the litigants or the taxpayers. A combined trial may be conducted on both the liability and the defense—similar to patent infringement cases where the plaintiffs present their infringement case at the same time as the defendants present their patent invalidity defense—particularly because the evidence presented will likely overlap. In sum, today's holding will not drastically change how defendants will litigate the preemption defense.

III. ANALYSIS

Having clarified the "clear evidence" standard, we now turn to the merits of Merck's preemption defense.[136]

Plaintiffs' causes of action fall into three groups. The first group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of atypical femur fractures by failing to add a warning to the Warnings and Precautions section of the label before September 2010 (the "Warnings and Precautions Claims"). The second group comprises Plaintiffs' claims that Merck failed to warn Fosamax users of the risk of femur fractures by failing to add atypical femur fractures to the Adverse Reactions section of the label prior to May 2009 (the "Adverse Reactions Claims"). The third group comprises all of

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[136] The District Court had subject matter jurisdiction under 28 U.S.C. § 1332. We have jurisdiction under 28 U.S.C. § 1291.

Plaintiffs' non-failure-to-warn claims, including design defect, negligence, breach of implied and express warranties, and violations of state consumer fraud and trade practice statutes (the "Non-Warning Claims"). The District Court ruled that the Warnings and Precautions claims were preempted under *Wyeth*; that the Adverse Reactions claims failed on the merits; and that the Non-Warning Claims were functionally indistinguishable from the Warnings and Precautions Claims and therefore preempted to the same extent.

Plaintiffs present four arguments on appeal. ***First***, Plaintiffs argue that the Warnings and Precautions Claims are not preempted as a matter of law because a reasonable jury could conclude that the FDA would have approved a properly worded atypical-fractures warning. ***Second***, Plaintiffs argue that Merck is not entitled to summary judgment on Plaintiffs' Adverse Reactions Claims because those claims were properly pleaded and there is sufficient evidence for a reasonable jury to find for the Plaintiffs. ***Third***, Plaintiffs argue that even if both sets of failure-to-warn claims are preempted, Plaintiffs' remaining claims are not preempted because they do not "sound in failure to warn" and are supported by competent evidence. ***Fourth***, Plaintiffs claim that the District Court misapplied Rule 56 when it tried to resolve Merck's affirmative preemption defense via a show-cause proceeding.

For the reasons set forth below, we conclude that (1) the Warnings and Precautions claims are not preempted as a matter of law because a reasonable jury could find it less than highly probable that the FDA would have rejected Plaintiffs' proposed

warning; (2) Merck is not entitled to summary judgment on the Adverse Reactions claims; and (3) the Non-Warning Claims are not preempted as a matter of law. Because we are vacating the District Court's summary judgment order, we do not reach the propriety of the show-cause order.

A. Summary Judgment Standard

Our review of a District Court's grant of summary judgment is plenary,[137] and we affirm only if "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law."[138] Because Merck moved for summary judgment, we must draw all reasonable inferences in the Plaintiffs' favor when considering the evidence.[139] Our inquiry is confined to "whether the evidence of record is such that a reasonable jury could return a verdict for the nonmoving party."[140] We therefore cannot grant summary judgment in Merck's favor "unless a reasonable juror would be compelled to find its way on the facts needed to rule in its favor on the law."[141]

Special considerations arise in the preemption context. Impossibility preemption is an affirmative defense[142] on which Merck bears the burdens of

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[137] *Reedy v. Evanson*, 615 F.3d 197, 210 (3d Cir. 2010).

[138] Fed. R. Civ. P. 56(a).

[139] *Anderson*, 477 U.S. at 255.

[140] *Reedy*, 615 F.3d at 210.

[141] *El v. Se. Pa. Transp. Auth.*, 479 F.3d 232, 238 (3d Cir. 2007).

[142] *PLIVA*, 564 U.S. at 634.

production and persuasion.[143] Crucially, "the inquiry involved in a ruling on a motion for summary judgment . . .necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits."[144] As discussed above, *Wyeth*'s "clear evidence" standard of proof requires the manufacturer to prove that it is *highly probable* that the FDA would not have approved a change to the drug's label. Therefore, the question for summary judgment purposes is not just whether a reasonable juror could find that the FDA would have approved Plaintiffs' proposed warning. It is whether a reasonable juror could find that it is highly probable that the FDA would have rejected the warning. Put differently: even if it seems possible or plausible that the FDA would have rejected the proposed warning, could a reasonable juror nonetheless conclude that the odds of rejection were something less than highly probable? In *El v. Southeastern Pennsylvania Transportation Authority*, we said that "if there is a chance that a reasonable factfinder would not accept a moving party's necessary propositions of fact, pre-trial judgment cannot be granted."[145] The corresponding proposition here is: if there is a chance that a reasonable factfinder would not find that it is highly probable that the FDA would have rejected Plaintiffs' warning, pre-trial judgment cannot be granted.

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[143] *El*, 479 F.3d at 237 & n.6.

[144] *Anderson*, 477 U.S. at 252.

[145] *El*, 479 F.3d at 238.

In summary: to affirm the District Court's decision that the Warnings and Precautions Claims are preempted, we must find that no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected Plaintiff's proposed atypical-fracture warning had Merck proposed it to the FDA in September 2010.

B. Merck is Not Entitled to Summary Judgment on Plaintiffs' Warnings and Precautions Claims

Merck's ultimate task under *Wyeth* is to prove by clear evidence that the FDA would not have approved the warning about the link between Fosamax use and atypical femur fractures that Plaintiffs say was required under state law. Merck's primary argument on appeal is that prior to September 2010, the FDA would have opposed *any* warning about atypical femur fractures in the Warnings and Precautions section because the FDA did not believe that the science supported such a warning. As Merck points out, the FDA sought and analyzed information regarding atypical femur fractures in 2008; Merck responded with data and then proposed warning language for both the Warnings and Precautions and Adverse Reactions sections of the Fosamax label; the FDA rejected Merck's proposed language for the Warnings and Precautions section; and in correspondence surrounding the rejection, FDA officials stated that the "conflicting nature of the literature does not provide a clear path forward," and "more time [would] be need[ed] for [the] FDA to formulate a formal opinion on the issue of a

precaution around these data."[146] Given this sequence of events, Merck argues that there is clear evidence that the FDA would not have approved a CBE submission adding an atypical-fracture warning to the Warnings and Precautions section.

It is undisputed that the FDA was aware of the possible link between Fosamax and atypical fractures well before September 2010. In March 2008, Merck submitted a comprehensive safety update to the FDA reporting the existence and results of numerous studies suggesting just such an association. The FDA responded that it was concerned about this "safety signal," but did not require Merck to update its label.[147] In March 2010, after reviewing the data submitted by Merck and other manufacturers, the FDA stated that the data reviewed to date had "not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."[148] And in October 2010, an FDA Deputy Director stated that the September 2010 task force report was the finding that for the first time made the FDA "confident" that atypical femur fractures are "potentially more closely related to" bisphosphonates "than [the FDA] previously had evidence for."[149] Merck argues that this evidence demonstrates that prior to September 2010, the FDA would have rejected *any* CBE application that attempted to add an atypical fractures warning to the Fosamax label

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[146] A 1971; *see also* A 1498.

[147] A 1935-36.

[148] A 1508.

[149] A 1396.

because the FDA had concluded that there was no reasonable evidence of a causal link.

Merck also emphasizes the FDA's April 2009 e-mail asking Merck to "hold off on the [Warnings and Precautions] language at this time" so that drug evaluators could "work with [the FDA's Office of Surveillance and Epidemiology] and Merck to decide on language for a [Warnings and Precautions] atypical fracture language, *if it is warranted.*"[150] After the task force issued its report in September 2010, by contrast, the FDA revised Merck's proposed language and quickly approved a label amendment. Merck argues that the "only logical conclusion from this course of proceedings is that the FDA thought adequate scientific support showing a connection between bisphosphonates and atypical femur fractures was lacking in 2009 but present in 2010 after the [task force] report, all of which accords with the FDA's public statements on the issue."[151]

Merck also rejects Plaintiffs' theory that the FDA rejected Merck's proposed warning based on a "language quibble" about stress fractures rather than a fundamental disagreement about the science. Merck's strongest argument for summary judgment is that Plaintiffs' theory of the case rests on an unreasonable inference: that the FDA (1) recognized a need to include risk information about atypical femur fractures and therefore would have accepted a properly-worded warning about such fractures, but (2) was so troubled by the "stress fracture" language

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[150] A 1498 (emphasis added).

[151] Merck Br. 50.

that it "preferred to deprive physicians of that risk information rather than allow Merck to add its proposed language or authorize inclusion of revised language."[152] Merck buttresses this argument by pointing to statutory language requiring the FDA to notify a drug manufacturer when it "becomes aware of new safety information that [it] believes should be included in the labeling of the drug" and to "initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information" if it is dissatisfied with the manufacturer's response.[153] Merck points out that if the FDA actually thought that an atypical-fracture warning was warranted, it could have proposed revisions rather than simply rejecting Merck's proposal. The FDA engaged in just such a revision process in 2010 after it directed Merck to add a warning and Merck responded by adding stress-fracture language. The fact that the FDA did not similarly reach out in 2009, Merck says, demonstrates that it would not have accepted Plaintiffs' proposed warning prior to the issuance of the task force report in September 2010.

We do not discount the force of this evidence or its potential to sway a jury. The problem for Merck, however, is that we are not assessing in the first instance whether there was clear evidence that the FDA would have rejected a change. We are instead trying to anticipate whether a reasonable juror, looking at all the evidence and trying to reconstruct a

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[152] *Id.* 48.

[153] 21 U.S.C. §§ 355(o)(4)(A) and (C).

hypothetical event, could conclude that it is less than highly probable that the FDA would have rejected the change. And crucially for the Plaintiffs, we are drawing all reasonable inferences in their favor. This confers a unique advantage when the factfinder's task is to guess what could have happened in a counterfactual setting.

Plaintiffs' argument against preemption centers on two claims: first, that there was sufficient evidence of a causal link to allow Merck to unilaterally amend the Fosamax label via the CBE process; and second, that the FDA's rejection of Merck's PAS application was based on Merck's misleading use of the term "stress fractures" rather than any fundamental disagreement with the underlying science. In our view, a reasonable jury could accept both contentions and conclude that the FDA would not have rejected Plaintiffs' proposed warning—or, at least, that the FDA was not highly probable to do so.

First, a reasonable jury could conclude that Merck could have amended the Fosamax label via the CBE process. To add a warning to the Warnings and Precautions section of a drug label through a CBE submission, "there need only be 'reasonable' evidence of a causal association with the drug, a standard that could be met by a wide range of evidence."[154] To gain FDA approval, therefore, the agency does not need to be affirmatively *convinced of* a causal link between the drug and the adverse event. Here, there is

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[154] 73 Fed. Reg. at 49,604. The same "reasonable evidence" standard that governs whether a manufacturer can submit a CBE application also governs whether the FDA should approve it. 21 C.F.R. § 201.57(c)(6)(i).

evidence that the FDA recognized a fracture risk and the possible need for warnings before September 2010. In June 2008, for example, the FDA stated that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates," that these and atypical femoral fractures were "reportedly rare in patients with osteoporosis not on bisphosphonates," and that it was "concerned about this developing safety signal."[155] And in May 2009, the FDA approved Merck's request to add a reference to "low energy femoral shaft and subtrochanteric fractures" in the Adverse Reactions section of the label.[156] Even if the FDA did not perceive a "clear connection" between Fosamax and atypical fractures, as it said in early 2010, a juror could conclude that the FDA would still have determined that "reasonable evidence" of a link existed—or more precisely, that the possibility of rejection was less than highly probable.

Second, a reasonable jury could also conclude that the FDA rejected Merck's proposed warning about femoral fractures in 2009 not because it denied the

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[155] A 1145.

[156] A 1500-01. As Plaintiffs point out, warnings can only be added to the Adverse Reactions section if they are "reasonably associated with use of" a drug and "there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." 21 C.F.R. § 201.57(c)(7) (FDA regulation describing requirements of "Adverse Reactions" section of label). A juror could therefore infer from the FDA's approval of the Adverse Reactions language that the FDA would have also agreed that there was "reasonable evidence of a causal association" between Fosamax and atypical femoral fractures.

existence of a causal link between Fosamax and fractures, but because Merck repeatedly characterized the fractures at issue as "stress fractures." Merck's proposed warning used the phrase "stress fractures" six times.[157] According to Plaintiffs' expert, stress fractures are commonly seen in physically active people; atypical femoral fractures

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[157] The following is the text of Merck's proposed addition to the Warnings and Precautions section, with references to "stress fractures" bolded:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. **Some were stress fractures** (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, **often associated with imaging features of stress fracture**, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and **stress fractures with similar clinical features also have occurred** in patients not treated with bisphosphonates. **Patients with suspected stress fractures** should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment. A 2720.

are, as the name suggests, highly unusual.[158] Stress fractures are usually incomplete fractures that heal with rest, while atypical femoral fractures often are complete fractures that require surgical intervention.[159] The FDA's response to Merck's PAS application stated: "Your justification for the proposed PRECAUTIONS section language is inadequate. Identification of 'stress fractures' may not be clearly related to the atypical subtrochanteric features that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting."[160] The FDA did not give any other reason for rejecting Merck's proposed warning.

In 2010, when Merck attempted to revise the FDA's proposed warning by adding references to stress fractures, the FDA again struck out the stress-fracture references. It explained that "the term 'stress fracture' was considered and was not accepted" because "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use."[161]

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[158] A 868 ¶ 22; A 881 ¶ 74; A 882 ¶ 76; *see also* A 1147 (task force report describing atypical femoral fractures as occurring with "relative rarity").

[159] A 884 ¶ 83-84; *see also* A 1149 (task force report describing atypical femoral fractures as "[c]omplete fractures").

[160] A 1500-01.

[161] A1540.

As discussed above, Merck argues that if the FDA had been truly concerned about the risk of atypical fractures, it could have revised and approved a warning without the offending stress-fracture references. As a matter of law, however, the burden and the responsibility to correct a drug label rests with the manufacturer, not the FDA.[162] Once the FDA rejected Merck's proposal, the ball was back in Merck's court to submit a revised, corrected proposal. A reasonable juror could therefore conclude that it was Merck's failure to re-submit a revised CBE or PAS without stress-fracture language, rather than the FDA's supposedly intransigent stance on the science, that prevented the FDA from approving a label change.

Plaintiffs' evidence certainly does not *compel* the conclusion that the FDA would have accepted an atypical fracture warning that omitted the language about stress fractures. But our inquiry at this stage is not about who has the best evidence; it is about what a reasonable jury applying a heightened standard of proof *could* conclude on the basis of the evidence. Because the *Wyeth* test requires the factfinder to speculate about hypothetical scenarios using inferences drawn from historical facts,

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[162] *See Wyeth*, 555 U.S. at 570-71 ("[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."); 21 U.S.C. § 355(o)(4)(I) ("Rule of construction" clarifying that the 2007 FDCA amendments "shall not be construed to affect the responsibility of the responsible person . . . to maintain its label in accordance with existing requirements").

reasonable jurors could reach a broad range of conclusions when confronted with this record. To that inherent uncertainty we then add all the reasonable inferences that Rule 56 requires us to draw in Plaintiffs' favor: the FDA would have agreed that the evidence of an association was "reasonable" prior to 2010; the FDA rejected Merck's proposed warning because it was primarily concerned with the misleading references to stress fractures rather than the underlying science; the FDA refrained from counter-proposing an acceptable warning in 2009 because it considered it Merck's responsibility to submit a revised warning; the FDA affirmatively reached out to Merck in 2010 because it recognized that the science was now so strong that amending the label was a legal imperative, not because it was acknowledging a sufficient risk for the first time.

A reasonable juror reviewing the evidence in this case could find it less than highly probable that the FDA would not have approved a warning about the risk of atypical femur fractures that eliminated or revised references to "stress fractures." Accordingly, Merck is not entitled to summary judgment on its preemption defense to Plaintiffs' Warnings and Precautions claims.[163]

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[163] Our ruling today concerns only the correctness of the District Court's March 24, 2014 decision that Merck was entitled to summary judgment on its affirmative preemption defense. We express no view as to whether or how our ruling should be applied to any individual action in the MDL going forward.

One of the reasons Merck gave for treating *Wyeth* preemption as a pure question of law was that doing so would allegedly ensure

C. Merck is Not Entitled to Summary Judgment on Plaintiffs' Adverse Reactions Claims

Plaintiffs' failure-to-warn claims focus primarily on the assertion that Merck should have added a fractures warning to the Warnings and Precautions

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consistency of its application across the hundreds of claims in this MDL. We of course do not decide issues by considering how many lawsuits our ruling will extinguish or revive. At any rate, the suits in this MDL pose numerous binary jury questions that conceivably apply across the board. Fosamax either causes atypical femoral fractures or it does not; Merck either knew about the alleged risks of fracture or it did not; the risks of Fosamax either outweighed its benefits or they did not; the list goes on. Ontologically speaking, there is an "objective" right answer to each of these questions that does not vary from case to case. And treating each issue as one of pure law to be disposed at a swoop of the judge's pen would certainly speed matters along. But neither consideration is an adequate basis to shift the traditional line between judge and jury functions. Of course, if the manufacturer shows that there is no genuine dispute as to any material fact bearing on *Wyeth* preemption, then a judge can indeed decide as a matter of law that the defense is established. But that showing was not made here. The FDA either would have approved Plaintiffs' warning or they would not; we cannot say.

Treating preemption as a jury issue does not automatically condemn Merck to a thousand individual jury trials. The MDL parties could, for example, hold a bellwether trial on the preemption question, after which the prevailing party would be free to argue that the other side should be collaterally estopped from re-litigating preemption in individual cases. *See Markman*, 517 U.S. at 391 (recognizing that treating a question as a factual issue does not leave it "wide open in every new court" because "principles of issue preclusion would ordinarily foster uniformity"). Again, we express no view on the merits or likely outcomes of such an approach.

section of the Fosamax label prior to September 2010. But Plaintiffs also contend that their failure-to-warn claims encompass a related but distinct allegation that Merck should have added atypical fractures to the Adverse Reactions section prior to May 2009 (the date the FDA actually approved Merck's addition of atypical fractures to the Adverse Reactions section), and that Merck's failure to do so proximately caused their injuries.[164] The District Court ruled that this claim was insufficiently pled and not supported by the evidence, and entered summary judgment for Merck on the merits. This ruling was in error.

As an initial matter, the Adverse Reaction Claims are not preempted by *Wyeth*, and Merck does not argue otherwise. Merck requested that atypical fractures be added to the Adverse Reactions section in 2009, and the FDA approved the request. Merck has not shown by clear evidence that the FDA would have rejected such a warning had Merck proposed it earlier.

Turning to the merits, the District Court dismissed the Adverse Reactions claims on two grounds.[165] The

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[164] *See* A 1501.

[165] Although it does not appear to have been a basis for its decision, the District Court observed that a large number of Plaintiffs alleged injuries occurring after the FDA added the Adverse Reactions warning. According to the District Court, these Plaintiffs would only be able to assert a failure-to-warn claim based on the absence of a warning in the Warnings and Precautions section of the label. We disagree, as these Plaintiffs remain free to argue that their injuries were caused by their *use* of Fosamax prior to the addition of the Adverse Reactions warning.

first basis for the District Court's ruling was its conclusion that Plaintiffs did not specifically plead a failure-to-warn claim based on the Adverse Reactions label section in any of their complaints. Whether or not this is an accurate assessment—we do not have every MDL complaint before us to confirm, and there is no indication that the District Court reviewed each of the hundreds of complaints at issue either—we think it beside the point. Plaintiffs direct us to a number of complaints alleging generally that the Fosamax label did not adequately warn patients and doctors of the fracture risk, without specifying the particular warnings that should have been included or the particular failings of each label section.[166] The parties and the District Court all accept that these general allegations adequately pled the Warnings and Precautions theory discussed above. It is therefore difficult to understand why the District Court faulted the same complaints for failing to specify every section of the label that should have included a warning. At any rate, such specificity is not required by the Federal Rules of Civil Procedure.[167] Merck does not argue that the complaints failed to put it on notice of the Adverse Reactions claim, and that concession closes the door on any claim that the complaints themselves failed to adequately plead the Adverse Reactions theory.

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[166] *See* A 2245 ¶ 54, 2249 ¶ 76, 2190 ¶ 123, 2333 ¶ 57.

[167] *See Oneida Indian Nation v. Cty. of Oneida*, 617 F.3d 114, 132 (2d Cir. 2010) (complaint need not specify the legal theory underlying its claims so long as it contains sufficient facts to support liability); *Kirksey v. R.J. Reynolds Tobacco Co.*, 168 F.3d 1039, 1041 (7th Cir. 1999) (same).

The District Court also stated, without elaboration, that Plaintiffs had failed to "set forth evidence indicating that any doctor would not have prescribed Fosamax if the occurrence of low-energy femoral shaft fractures had been mentioned in the Adverse Reactions section prior to 2009."[168] Even if true, this does not justify summary judgment on the merits. The proper inquiry for summary judgment purposes is whether there was sufficient evidence to permit a reasonable juror to conclude that a doctor would not have prescribed Fosamax if fracture language had been added to the Adverse Reactions section prior to 2009. To this end, Plaintiffs submitted several declarations from their treating physicians declaring that if they had been informed that Fosamax posed a risk of femoral fractures, they likely would not have prescribed Fosamax or likely would have discontinued treatment.[169] These declarations do not specify which sections of the label should have contained such a warning. A reasonable juror could conclude that some of these physicians would not have prescribed Fosamax if atypical femur fractures had been listed in the Adverse Reactions section. Accordingly, the District Court should not have granted Merck summary judgment on the merits of Plaintiffs' Adverse Reactions failure-to-warn claims.

There is a deeper problem lurking in the District Court's decision to grant Merck a merits judgment in all of the MDL cases. A mass tort MDL is not a class action. It is a collection of separate lawsuits that are

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[168] Summary Judgment Order, 2014 WL 1266994, at *15.

[169] *See, e.g.*, A 792 ¶ 10, 794 ¶ 9, 796-97 ¶ 9, 798 ¶ 8.

coordinated for pretrial proceedings—and *only* pretrial proceedings—before being remanded to their respective transferor courts.[170] Some purely legal issues may apply in every case. But merits questions that are predicated on the existence or nonexistence of historical facts unique to each Plaintiff—*e.g.*, whether a particular Plaintiff's doctor would have read a warning in the Adverse Reactions section and ceased prescribing Fosamax as a result—generally are not amenable to across-the-board resolution. Each Plaintiff deserves the opportunity to develop those sort of facts separately, and the District Court's understandable desire to streamline proceedings cannot override the Plaintiffs' basic trial rights.[171] As a technical matter, Merck's *actual* burden at the summary judgment stage was to prove that there is no genuine dispute in *every single MDL case* that Plaintiffs' doctors would have continued to prescribe Fosamax even if the fracture warning had been added to the Adverse Reactions section before May 2009. It could not do so, and the District Court's grant of summary judgment on the merits was therefore erroneous.

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[170] 28 U.S.C. § 1407(a).

[171] The District Court and the parties could have, but did not, choose to have the Plaintiffs assemble a single "master complaint" that superseded the individual complaints. *See In re Refrigerant Compressors Antitrust Litig.*, 731 F.3d 586, 590-91 (6th Cir. 2013).

D. Merck is Not Entitled to Summary Judgment on Plaintiffs' Non-Warning Claims

The District Court held that Plaintiffs' Non-Warning Claims sounded in failure to warn and were therefore preempted to the same extent as the Warning and Precautions Claims. Accordingly, our decision vacating the District Court's preemption ruling as to the Warnings and Precautions Claims reinstates the Non-Warning Claims as well.[172] We pass no judgment on the merits of those claims or on whether they do in fact sound in failure to warn.

IV. CONCLUSION

For the foregoing reasons, we will vacate the District Court's grant of summary judgment to Merck and remand for further proceedings consistent with this opinion.

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[172] Merck argues that the non-warning claims are separately preempted by the Supreme Court's decision in *Mutual Pharmaceutical Co. v. Bartlett*, 133 S. Ct. 2466 (2013). Merck admits, however, that it did not raise this argument below—indeed, Merck appears to have explicitly disavowed the argument so it could characterize its defense as being based solely on *Wyeth*. Merck Br. 68; A 1727-28. "It is well established that arguments not raised before the District Court are waived on appeal." *DIRECTV Inc. v. Seijas*, 508 F.3d 123, 125 n.1 (3d Cir. 2007). We see no reason to deviate from that rule here.

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Brown, Towanda	14-2411	3-12-cv-02600
Tressler, Vera	14-2412	3-12-cv-02647
Heldberg, Judith	14-2413	3-12-cv-02771
Hen, Azucena	14-2414	3-12-cv-02833
Sias, Diana Van Pelt	14-2415	3-12-cv-02837
Otto, Harriet	14-2416	3-12-cv-02838
Best, Bettie	14-2417	3-12-cv-03017
Davis, Betty Saki	14-2418	3-12-cv-03021

Roberts, Margaret	14-2419	3-12-cv-03022
Goias, Geraldine	14-2420	3-12-cv-03023
Lona, Lucille	14-2421	3-12-cv-03025
McMurray, Deborah	14-2422	3-12-cv-03026
Doriott, Angelita	14-2423	3-12-cv-03027
Thieman, Donna	14-2424	3-12-cv-03259
White, Claudia	14-2425	3-12-cv-03260
Eshelman, Stephanie	14-2426	3-12-cv-03261
Grillo, Maria	14-2427	3-12-cv-03286
Stefanowski, Lucy	14-2428	3-13-cv-07894
Burghardt, Pamela	14-2429	3-12-cv-03326
Gerber, Marilyn	14-2430	3-12-cv-03328
Tong, Lucy	14-2431	3-12-cv-03329
Venner, Vida	14-2432	3-12-cv-03330
Uslan, Sharon	14-2433	3-12-cv-03331
Goldberg, Ethel	14-2434	3-12-cv-03335
Hudson, Laraine	14-2435	3-12-cv-03345
Rittenhouse, Carolyn	14-2436	3-12-cv-03346
Budd, Randal	14-2437	3-12-cv-03347
Myers, Eva	14-2438	3-12-cv-03348
Dykes, Marsha	14-2439	3-12-cv-03358
Foree, Edith	14-2440	3-12-cv-3366
Indich, Terry	14-2441	3-12-cv-03399
Travor, Lois Annette	14-2442	3-12-cv-03429
Steen, Barbara	14-2443	3-12-cv-03511
Charms, Shirley	14-2444	3-12-cv-03696

Denham, Janice	14-2445	3-12-cv-03705
Tanglao, Lourdes	14-2446	3-12-cv-03730
Disosway, Linda	14-2447	3-12-cv-03769
Lare, Sandra	14-2448	3-12-cv-03770
Nealen, Arlene	14-2449	3-12-cv-03789
DerHarootunian, Car[olyn]	14-2450	3-12-cv-03795
Yacoub, Caroline	14-2452	3-12-cv-03878
Baker, Alma	14-2453	3-12-cv-03879
Palma, Lucita	14-2454	3-12-cv-03904
Mateo, Yoshie	14-2455	3-12-cv-03939
Terranova. Patricia	14-2456	2-12-cv-03959
Hill, Mary	14-2457	3-12-cv-04014
Wilson, Selma	14-2458	3-12-cv-04190
Toland Kathleen	14-2459	3-12-cv-04423
Fillippello, Margaret	14-2460	3-12-cv-04424
Harris, Ramona	14-2461	3-12-cv-04426
Lane, Sharon	14-2462	3-12-cv-04440
Whisenant, Louise	14-2463	3-12-cv-04453
Carter, Joan	14-2464	3-12-cv-04454
Glenn, Sue	14-2465	3-12-cv-04566
Sweet, Karen	14-2466	3-12-cv-04599
Hutton, Nancy	14-2467	3-12-cv-04601
Hernandez, Antonia	14-2468	3-12-cv-04604
Favor, Judith	14-2469	3-12-cv-04611
Parker, Esther	14-2471	3-12-cv-04638

Mitchell, Cheryl	14-2472	3-12-cv-04656
Paralikis, Pamela	14-2473	3-12-cv-04663
Bottari, Donna	14-2474	3-12-cv-04664
Hedgepeth, Betty	14-2475	3-12-cv-04721
Sperber, Bernice	14-2476	3-12-cv-04760
Currie, Marlene	14-2477	3-12-cv-04762
Worthington, Jerrene	14-2478	3-12-cv-04773
Patrina, Chester []	14-2479	3-12-cv-04802
Falcone, Patricia	14-2480	3-12-cv-04806
Anselmo, Victoria	14-2481	3-12-cv-04836
Patterson, Ethel	14-2482	3-12-cv-05018
Haslam, Martha	14-2483	3-12-cv-05019
Julius, Diana	14-2484	3-12-cv-05020
Mott, Leann	14-2485	3-12-cv-05060
Theberge, Jeanne	14-2486	3-12-cv-05085
Walker, Shirley	14-2487	3-12-cv-05094
Bedsworth, Alan []	14-2488	3-12-cv-05108
Crew, Nellie	14-2489	3-12-cv-05205
Astrug, Debra	14-2490	3-12-cv-05269
Dixon, Carolyn	14-2491	3-12-cv-05271
Edgil-Rogers, Judee	14-2492	3-12-cv-05297
Gilmer, Marjorie	14-2493	3-12-cv-05364
Kovalick, Carole	14-2494	3-12-cv-05383
Knutson, Josephine	14-2495	3-12-cv-05384
Smith, Regina	14-2496	3-12-cv-05385

Hamilton-Gamman, S[andra]	14-2497	3-12-cv-05389
Needles, Josephine	14-2498	3-12-cv-05391
Kendrick. Billie	14-2499	3-12-cv-05392
Paxton, Mary	14-2500	3-12-cv-05393
Stanwood, Peggy	14-2501	3-12-cv-05485
Knopick, Carol	14-2502	3-12-cv-05557
Osburn, Gaile	14-2503	3-12-cv-05560
Miller, Dolores	14-2504	3-12-cv-02549
Heckard, Shirley	14-2505	3-12-cv-05681
Cline, Diane	14-2506	3-12-cv-05776
Cummings, Sarah	14-2507	3-12-cv-05975
Jodszuweit, Armida	14-2508	3-12-cv-05978
Collier, Nancy	14-2509	3-12-cv-05993
Sayers, Sheila	14-2510	3-12-cv-06028
Cook. Shirley	14-2511	3-12-cv-06029
Wiegand, Mary	14-2512	3-12-cv-06155
Roland, Annie	14-2513	3-12-cv-06182
Bridgeman, Max	14-2514	3-12-cv-06187
Wong, Anita	14-2515	3-12-cv-06191
Hayden, Jane	14-2516	3-12-cv-06192
McGrath, Sheila	14-2517	3-12-cv-06216
Van Blaricom, Betty	14-2518	3-12-cv-06237
Thomas, Eugune Mid[dleton]	14-2519	3-12-cv-06264
Fuerstnau, Barbara	14-2520	3-12-cv-06266
Halfmann, Mary	14-2521	3-12-cv-06267

Kimizuka, Yoshie	14-2522	3-12-cv-06269
Hofmann, Kathleen	14-2523	3-12-cv-06275
Duggan, Doris	14-2524	3-12-cv-06289
Andorka-Aceves, Deb[orah]	14-2525	3-12-cv-06301
Herndon, Lucy Mae	14-2526	3-12-cv-06351
Delikat. Ellen	14-2527	3-12-cv-06365
Mouser, Donna	14-2528	3-12-cv-06366
Hulsman, Elaine	14-2529	3-12-cv-06376
Kempfer, Faye	14-2530	3-12-cv-06377
Lotter, Dolores	14-2531	3-12-cv-06378
Cummings, Irene Lilli[an]	14-2532	3-12-cv-06397
Irving, Zepher	14-2533	3-12-cv-06430
Marcus, Rita	14-2534	3-12-cv-06432
Halpern, Marion	14-2535	3-12-cv-06433
Ogle, Ann	14-2536	3-12-cv-06434
Bittner, Marcella	14-2537	3-12-cv-06437
Wade, Kay	14-2538	3-12-cv-06439
Ahern, Frances	14-2539	3-12-cv-06443
Boshell, Marsha	14-2540	3-12-cv-06444
Sandt, Faye	14-2541	3-12-cv-06445
Holmes, Leanne	14-2542	3-12-cv-06446
Napoli, Anna	14-2543	3-12-cv-06450
Vaughn, Patricia	14-2544	3-12-cv-06451
Irizarry, Sheila	14-2545	3-12-cv-06453
Kort, Barbara	14-2546	3-12-cv-06454

Kosvick. Melinda	14-2547	3-12-cv-06455
Homa. Barbara	14-2548	3-12-cv-06456
Stepanski, Mary Jo	14-2549	3-12-cv-06457
Lare, Barbara	14-2550	3-12-cv-06458
Nguyen, Susan	14-2551	3-12-cv-06459
Jeet, Lalita	14-2552	3-12-cv-06460
Naik, Khadijah	14-2553	3-12-cv-06461
Bartlett, Ann	14-2554	3-12-cv-06462
Aydin. Jean	14-2555	3-12-cv-06463
Dowd, Jeanette	14-2556	3-12-cv-06464
Van Gosen, Helen	14-2557	3-12-cv-06465
Huddleston, Shirley	14-2558	3-12-cv-06466
Griffin. Jennifer	14-2559	3-12-cv-06469
Crisci, Stephen N. []	14-2560	3-12-cv-06550
Jones, Geraldine	14-2561	3-12-cv-06711
McKinney, Carlene	14-2562	3-12-cv-06719
Karantza, John	14-2563	3-12-cv-06770
Bozue, Dorothy	14-2564	3-12-cv-06840
Cline, Beatrice	14-2565	3-12-cv-06841
Broadstone, Judith	14-2566	3-12-cv-06845
Schmitt, Luise Gerlin[de]	14-2567	3-12-cv-06846
Cherco. Patricia	14-2568	3-12-cv-06850
Neuman, Janet	14-2569	3-12-cv-06859
Isom, Leann	14-2570	3-12-cv-06860
Heiny, Joyce	14-2571	3-12-cv-06863

Vertuccio, Lana	14-2572	3-12-cv-06877
Williams, Susanne	14-2573	3-12-cv-06899
Stevenson, Nada	14-2574	3-12-cv-06900
Elison, Linda	14-2575	3-12-cv-06901
Lingo, Melba	14-2576	3-12-cv-06903
Baylor, Richard	14-2577	3-12-cv-06905
Thompson, Loralee	14-2578	3-12-cv-06907
Miller, Esther	14-2579	3-12-cv-06952
Orr, June	14-2580	3-12-cv-06954
Maki, Gale	14-2581	3-12-cv-06955
Collins, John	14-2582	3-12-cv-06956
McAnulty, Joan	14-2583	3-12-cv-06957
Abney, Virginia	14-2584	3-12-cv-07023
Altson, Amy	14-2585	3-12-cv-07048
Harris, Hope []	14-2586	3-12-cv-07443
Jaeger, Bernadette	14-2587	3-12-cv-07819
Couture, Diane	14-2588	3-13-cv-00001
VanDyke, Patricia	14-2589	3-13-cv-00137
Antoff, Christine	14-2590	3-13-cv-00171
Wyly, Lois Ann	14-2592	3-13-cv-00442
Conner, Cheryl	14-2593	3-13-cv-00718
Kardon, Koula	14-2594	3-13-cv-00720
Bialkowski, Mary	14-2595	3-13-cv-00816
Affronti, Joanne	14-2599	3-13-cv-00818
Bannon, Gladys	14-2600	3-13-cv-00894
Golden, Jane	14-2601	3-13-cv-00926

Pitts, Shirley Ann	14-2602	3-13-cv-00928
Slinkman, William Ric[hard]	14-2603	3-13-cv-01062
Albert, Elizabeth	14-2604	3-13-cv-01063
Hawk, Joycelyn	14-2605	3-13-cv-01071
Pritchard, Helen	14-2606	3-13-cv-01215
Myers, Susan	14-2607	3-13-cv-01314
Brooks, Betty	14-2608	3-13-cv-01337
Hawkins, Amy	14-2609	3-13-cv-01340
Edmondson, Maxine	14-2610	3-13-cv-01352
Kamienski, Mary	14-2611	3-13-cv-01369
Neuman, Delores	14-2612	3-13-cv-01370
Peters, Alohoa	14-2613	3-13-cv-01371
Routhieaux, Marguer[itte]	14-2614	3-13-cv-01378
Alberg, Evelyn	14-2615	3-13-cv-01415
Goodman, Carol Ann	14-2616	3-13-cv-01476
Samuelson, Johann	14-2618	3-13-cv-01884
Rudolph, Joyce	14-2619	3-13-cv-02616
Romeo, Alice	14-2620	3-13-cv-02617
Grems, Mary	14-2621	3-13-cv-2649
McKeon-Cincotta, Le[na]	14-2622	3-13-cv-02735
Jernigan, Mary Lou	14-2623	3-13-cv-02827
Wicker, Marie	14-2624	3-13-cv-02836
Stampliakis, Helen	14-2625	3-13-cv-02958
Crook, Judith	14-2626	3-13-cv-03211

London, Phyllis	14-2627	3-13-cv-03342
Connor, Ruth	14-2628	3-13-cv-03353
Mulqueen, Mary	14-2629	3-13-cv-03474
Bergmann, Ruth	14-2630	3-13-cv-03741
Spallone, Josephine	14-2631	3-13-cv-03929
Maddern, Karen	14-2632	3-13-cv-04075
Marcelles, Sara	14-2634	3-13-cv-05984
Tolston, Betty	14-2635	3-13-cv-06090
Oakes, Miriam	14-2636	3-11-cv-05082
Murphy, Nancy	14-2813	3-12-cv-06282
Gaynor, Barbara	14-3267	3-12-cv-01492

APPENDIX B

UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 14-1900 et al

In re: Fosamax (Alendronate Sodium) Product Liability Litigation

ORDER AMENDING APPENDIX A TO OPINION

Due to inadvertent clerical errors, Appendix A to the opinion was missing one appeal number (14-3220) and a lower court number (08-cv-00008). The Appendix has been revised and the corrected version will be filed as an attachment to this order.

For the Court,

s/ Marcia M. Waldron
Clerk

Dated: April 11, 2017
PDB/cc: All Counsel of Record

Appendix A

Case Name	Appeal No.	DNJ No.
Albrecht, Doris	14-1900	3-12-cv-03287
Molnar, Phyllis	14-2109	3-08-cv-00008
Gozdziak, Margaret	14-2110	3-09-cv-05630
Duke, Dolores	14-2111	3-09-cv-05693
Schultz, Susan	14-2112	3-08-cv-03545
Hines, Cynthia	14-2113	3-10-cv-04839
Goodwin, Joan	14-2114	3-10-cv-05461
Moline, Barbara	14-2115	3-10-cv-05462
Wheeler, Kathryn	14-2117	3-10-cv-06282
Denker, Elayne	14-2118	3-11-cv-00033
Heaton, Nancy	14-2119	3-11-cv-00570
Bonne, Virginia	14-2120	3-11-cv-00571
Lefebvre, Alice	14-2121	3-11-cv-00586
Hogan, Marie	14-2122	3-11-cv-00587
Karch, Lillie	14-2123	3-11-cv-00589
Walraed, Susan	14-2124	3-11-cv-00869
Kolb, Lauren	14-2126	3-11-cv-01498
Dematto, Mary	14-2127	3-11-cv-01886
Germino, Virginia Lee	14-2128	3-11-cv-03165
Chaires, Jeanette	14-2129	3-11-cv-03168
Salvatore, Sheila	14-2130	3-11-cv-03169
Collins, Lucille	14-2131	3-11-cv-03170
Miller, Betty	14-2132	3-11-cv-03174
Young, Marilyn	14-2133	3-11-cv-03225
Sunshine, Beverly	14-2134	3-11-cv-03309
Sutton, Barbara	14-2135	3-11-cv-03310
Granato, Irene	14-2136	3-11-cv-03369
Graves, Barbara	14-2137	3-11-cv-03645
Brown, Elizabeth	14-2138	3-11-cv-03867
Van, Mary Evelyn	14-2139	3-11-cv-03911

Zessin, Deloris	14-2140	3-11-cv-03919
Wirth, Carol	14-2141	3-11-cv-03930
Lyman, Patricia	14-2142	3-11-cv-04160
Foley, Peggy	14-2143	3-11-cv-04171
O'Brien, Molly	14-2144	3-11-cv-04242
O'Brien, Molly	14-2145	3-11-cv-04242
Evans, Laura	14-2146	3-11-cv-04277
Krieg, Julia	14-2147	3-11-cv-04956
Cortez, Lorice	14-2148	3-11-cv-05025
Hardy, Shirley	14-2149	3-11-cv-05077
Marks, Martha	14-2150	3-11-cv-05079
Grassucci, Shirley	14-2151	3-11-cv-05083
Clougherty, Mary Pat[ricia]	14-2153	3-11-cv-05295
Edwards, Sybil	14-2154	3-11-cv-05300
Johnson, Susan	14-2155	3-11-cv-05301
Onaka, Eleanor	14-2156	3-11-cv-05302
Scott, Sylvia	14-2157	3-11-cv-05303
Whitt, Betty Jean	14-2158	3-11-cv-05335
Penigian, Jean	14-2159	3-11-cv-05703
Berlin, Ruth	14-2160	3-11-cv-05720
Collins, Joann	14-2161	3-11-cv-05826
Brogna, Loretta	14-2162	3-11-cv-05912
Hodge, Helen	14-2163	3-11-cv-06162
Stark, Vivian	14-2164	3-11-cv-06164
Voss, Betty	14-2165	3-11-cv-06347
Schornick, Lori []	14-2166	3-11-cv-06387
Panouis, Androniki	14-2167	3-11-cv-06411
Blackford, June	14-2168	3-11-cv-06415
Krakovitz, Pearl	14-2169	3-11-cv-06417
Pisarz, Josephine	14-2170	3-11-cv-06419
Strominger, Betty	14-2171	3-11-cv-06420
Schick, Joan	14-2172	3-11-cv-06421
Chee, Paula	14-2173	3-11-cv-06451

Gribben, Angela	14-2174	3-11-cv-06452
Ourecky, Roberta	14-2175	3-11-cv-06468
Price, Carolyn	14-2176	3-11-cv-06469
Howe, Elaine	14-2177	3-11-cv-06657
Care, Margaret	14-2178	3-11-cv-06694
Hanel, Kannika	14-2179	3-11-cv-06817
Standish, Debbie	14-2180	3-11-cv-06912
Wilkins, Edith	14-2181	3-11-cv-06945
Covey, Janet	14-2182	3-11-cv-06946
Radford, Shirley	14-2183	3-11-cv-06947
Poynor, Sherry	14-2184	3-11-cv-06948
Johnson, Janet	14-2185	3-11-cv-06959
Sontag, Marian	14-2186	3-11-cv-06983
Nelson, Edward	14-2187	3-11-cv-07020
Haviland, Barbara	14-2188	3-11-cv-07104
Matney, Rosemary	14-2189	3-11-cv-07145
McGill, Barbara	14-2190	3-11-cv-07185
Schwalbe, Linda	14-2191	3-11-cv-07208
Nation, Karleen	14-2192	3-11-cv-07345
Misner, Anita	14-2193	3-11-cv-07401
Burke, Louise	14-2194	3-11-cv-07429
Carter-Morcomb, Pat[ty]	14-2195	3-11-cv-07432
Messerli, Donna	14-2196	3-11-cv-07491
McKee, Eleanor	14-2197	3-11-cv-07493
Mayes, Claudice	14-2198	3-11-cv-07516
Joyce, Michael	14-2199	3-11-cv-07517
Hensley, Mary	14-2200	3-11-cv-07518
Degen, Patricia	14-2201	3-11-cv-07519
Mahan, Caroline	14-2202	3-11-cv-07520
Mistretta, Wilma	14-2203	3-11-cv-07521
Sorrentino, Theresa	14-2204	3-11-cv-07522
Tucker, Assunta	14-2205	3-11-cv-07523
Green, Mariella	14-2206	3-11-cv-07524

Greenway, Ann	14-2207	3-11-cv-07525
Ivey, Jane	14-2208	3-11-cv-07557
Driver, Virginia	14-2209	3-11-cv-07558
Juth, Joann	14-2210	3-11-cv-07613
Buitron, Catherine	14-2211	3-11-cv-007614
Wallis, Russell	14-2212	3-11-cv-07619
Carter, Ann	14-2213	3-12-cv-00012
Murphy, Betty	14-2214	3-12-cv-00014
Sutton, Catrinia []	14-2215	3-12-cv-00015
Duffy, Joan	14-2216	3-12-cv-00016
Pinkney, Lani	14-2217	3-12-cv-00017
Nagy, Norma	14-2218	3-12-cv-00018
Richardson, Lee	14-2219	3-12-cv-00019
Skinner, Leone	14-2220	3-12-cv-00021
Steinert, Julie	14-2221	3-12-cv-00022
Lopes, Mary	14-2222	3-12-cv-00023
Shepherd, Madge	14-2223	3-12-cv-00082
Pappas, Diane []	14-2224	3-12-cv-00168
Anderson, Barbara []	14-2225	3-12-cv-00227
Nesbitt, Craig	14-2226	3-12-cv-00268
Coventry, Melinda	14-2227	3-12-cv-00269
Adams, Brenda	14-2228	3-12-cv-00270
Yancu, Milly	14-2229	3-12-cv-00271
Franklin, Suzane	14-2230	3-12-cv-00272
Davis, Patricia	14-2231	3-12-cv-00273
Foland, Bobbie []	14-2232	3-12-cv-00278
Gerardo, Claudia	14-2233	3-12-cv-00310
Mueller, Eileen	14-2234	3-12-cv-00312
Held, Mary	14-2235	3-12-cv-00360
Weiss, Linda	14-2236	3-12-cv-00374
Hunt, Betty Burch	14-2237	3-12-cv-00375
Eisen, Ella	14-2239	3-12-cv-00391
Rangel, Elvia	14-2240	3-12-cv-00392

Thomasson, Patsy M[ay]	14-2241	3-12-cv-00403
Schendle, Carolyn	14-2242	3-12-cv-00404
Hogan, Charlotte	14-2243	3-12-cv-00464
Baldridge, Wilemina	14-2244	3-12-cv-00503
McCabe, Doreen	14-2245	3-12-cv-00504
McCabe, Judith	14-2246	3-12-cv-00508
Huenefeld, Catherine	14-2247	3-12-cv-00564
Gregori, Carolyn	14-2248	3-12-cv-00566
Heinonen, Marie	14-2249	3-12-cv-00567
Rath, Carolyn	14-2250	3-12-cv-00568
Rousey, Shirlie	14-2251	3-12-cv-00569
Simpson, Esther	14-2252	3-12-cv-00570
Wilson, Sharon	14-2253	3-12-cv-00571
Stotts, Wilma	14-2254	3-12-cv-00572
Everly, Myrna	14-2255	3-12-cv-00588
Kraynick, Judith	14-2256	3-12-cv-00589
Begany, Helen	14-2257	3-12-cv-00590
Finn, Barbara	14-2258	3-12-cv-00591
Scott, Lois	14-2259	3-12-cv-00592
Migatulski, Mary	14-2260	3-12-cv-000593
Reitz, Alice	14-2261	3-12-cv-00594
Cooper, Eva	14-2262	3-12-cv-00595
Delagarza, Margaret	14-2263	3-12-cv-00622
Shapiro, Ellen	14-2264	3-12-cv-00623
Frangos, Artemis	14-2265	3-12-cv-00625
Freelin, Stephanie	14-2266	3-12-cv-00626
Grassel, Sara	14-2267	3-12-cv-00627
Halpern, Beverly	14-2268	3-12-cv-00628
Harvey, Robert	14-2269	3-12-cv-00629
Jones, Renae	14-2270	3-12-cv-00631
Singh, Priscilla	14-2271	3-12-cv-00640
Worthington, Renee	14-2272	3-12-cv-00643
Palmer, Richard	14-2273	3-12-cv-00644

James, Claudia	14-2274	3-12-cv-00645
Kozloski, Margaret	14-2275	3-12-cv-00647
Matthews, Roxie Mo[gler]	14-2276	3-12-cv-00648
Newman, Lula	14-2277	3-12-cv-00649
Dirks, Susan	14-2278	3-12-cv-00650
Carpenter, Julia Ann	14-2279	3-12-cv-00651
Madary, Roberta	14-2280	3-12-cv-00654
Rimstidt, Nelda	14-2281	3-12-cv-00655
Taylor, Sherri	14-2282	3-12-cv-00656
Balsam, Barbara	14-2283	3-12-cv-00657
Mester, Dorothy	14-2284	3-12-cv-00658
Raven, Arleen	14-2285	3-12-cv-00659
Garrett, Barbara	14-2286	3-12-cv-00660
Dwyer, Marion	14-2287	3-12-cv-00663
Eck, Marlene	14-2288	3-12-cv-00664
Uselton, Lynnita	14-2289	3-12-cv-00665
Still, Nanette	14-2290	3-12-cv-00666
Wheeler, Jo	14-2291	3-12-cv-00667
Smith, Richard	14-2292	3-12-cv-00688
Bucher, Rose	14-2293	3-12-cv-00689
Giarratano, Ruth	14-2294	3-12-cv-00690
Goheen, Patty	14-2295	3-12-cv-00691
Powers, Peggy	14-2296	3-12-cv-00692
Muller, Eleanor	14-2297	3-12-cv-00693
Lemley, Sheila	14-2298	3-12-cv-00694
Curry, Nellie	14-2299	3-12-cv-00695
Thomas-Walsh, Ther[esa]	14-2300	3-12-cv-00707
Swanson, Nancy	14-2301	3-12-cv-00714
Erickson, Doris	14-2302	3-12-cv-00715
Pearson, Linda	14-2303	3-12-cv-00750
Underhill, Mary Lee	14-2304	3-12-cv-00762
Nord, Elayne Barbara	14-2305	3-12-cv-00789

Bryant, Jane	14-2306	3-12-cv-00790
Ciraolo, Joanna	14-2307	3-12-cv-00791
Savoy, Josephine	14-2308	3-12-cv-00855
Gentile, Emma	14-2309	3-12-cv-00928
Factor, Rosalyn Rena	14-2310	3-12-cv-00936
Walker, Sherry	14-2311	3-12-cv-00943
McCune, Bonnie	14-2312	3-12-cv-00950
Meldon, Virginia	14-2313	3-12-cv-00974
Greenberg, Carla	14-2314	3-12-cv-01009
Armstrong, Bobbie	14-2315	3-12-cv-01013
Garman, Rose Ann	14--2316	3-12-cv-01020
Goggin, Carol	14-2317	3-12-cv-01021
Goodman, Susan Jan[e]	14-2318	3-12-cv-01035
Drouet, Renee	14-2319	3-12-cv-01036
Stroh, Kerry	14-2320	3-12-cv-01038
Medina, Laarni	14-2321	3-12-cv-01065
Whitman, Ethel	14-2322	3-12-cv-01075
D'Angelo, Kimiko	14-2323	3-12-cv-01093
Hollander, Carol	14-2324	3-12-cv-01107
Harrow, Ronnie	14-2325	3-12-cv-01111
Hardy, Yvette	14-2326	3-12-cv-01132
Lynn, Vivian	14-2327	3-12-cv-01133
Hill, Laura Lee	14-2328	3-12-cv-01134
Gitter, Blossom	14-2329	3-12-cv-01135
Clow, Edna	14-2330	3-12-cv-01177
Hulik, Linda	14-2331	3-12-cv-01179
Lyons, Janet	14-2332	3-12-cv-01180
Fitzpatrick, Nora	14-2333	3-12-cv-01181
Suehiro, Tokia	14-2334	3-12-cv-01185
Brown, Linton	14-2335	3-12-cv-01186
Seims, Marcie	14-2336	3-12-cv-01187
Andrejasich, Anne	14-2337	3-12-cv-01200
Edwards, Sally	14-2338	3-12-cv-01203

Kakareka, Edith	14-2339	3-12-cv-01204
Jones, Denman	14-2340	3-12-cv-01205
Morris, Joyce	14-2341	3-12-cv-01220
Murphy, Cheryl	14-2342	3-12-cv-01221
Spires, Evelyn	14-2343	3-12-cv-01222
Davis, Anna M.	14-2345	3-12-cv-01277
Jefferies, Gail	14-2346	3-12-cv-01322
Ross, Betty Jo	14-2347	3-12-cv-01325
Jepson, Norma	14-2348	3-12-cv-01326
Fifer, Ladonna	14-2349	3-12-cv-01327
Moore, Marlene	14-2350	3-12-cv-01328
Bryant, Sharon	14-2351	3-12-cv-01329
Bishop, Rosemary	14-2352	3-12-cv-01344
Burleson, Jacqueline	14-2354	3-12-cv-01356
Fenton, Carole	14-2355	3-12-cv-01373
Yost, Marilyn	14-2356	3-12-cv-01387
Richard-Amato, Patri[cia]	14-2357	3-12-cv-01395
Wang, Su-Mei	14-2358	3-12-cv-01397
Zimmerman, Martha [Farr]	14-2359	3-12-cv-01398
Flower, Gail	14-2360	3-12-cv-01399
Cross, Katherine	14-2361	3-12-cv-01410
Mejia, Teresita	14-2362	3-12-cv-01449
Agrow, Rosalie	14-2363	3-12-cv-01450
Crook, Patricia	14-2364	3-12-cv-01468
Courville, Paula	14-2365	3-12-cv-01476
Bielecky, Margaret	14-2366	3-12-cv-01484
Wright, Judith	14-2367	3-12-cv-01487
Hayes, Mavis	14-2368	3-12-cv-01549
Hanson, Nelda	14-2369	3-12-cv-01552
Stencler, Roxanna	14-2370	3-12-cv-01566
Lowell, Sarah	14-2371	3-12-cv-01567
Collier, Marion	14-2372	3-12-cv-01568

Waldrup, Roberta	14-2373	3-12-cv-01569
Bohn, Edward []	14-2375	3-12-cv-01715
Freay, Onnolee	14-2376	3-12-cv-01754
Sheehan, Yvonne T[.]	14-2377	3-12-cv-01817
Merrell, Preston	14-2378	3-12-cv-01845
Jones, Alice	14-2379	3-12-cv-01846
Fracaro, Fern Lee	14-2380	3-12-cv-01847
McKelvey, Elizabeth	14-2381	3-12-cv-01849
Keaser, Barbara	14-2382	3-12-cv-01850
Brenner, Lois	14-2383	3-12-cv-01875
Azar, Bernice	14-2384	3-12-cv-01876
Hubbard, Linda	14-2385	3-12-cv-01967
Arnold, Doris	14-2386	3-12-cv-01975
Halligan, Carla	14-2387	3-12-cv-01996
Frei, Miryam	14-2388	3-12-cv-01997
Besser, Deborah []	14-2389	3-12-cv-01998
Dandridge, Earlene	14-2390	3-12-cv-01999
Weissberger, Kathryn	14-2391	3-12-cv-02000
Stone, Harriet	14-2392	3-12-cv-02002
Pustilnik, Jean	14-2393	3-12-cv-02048
Pickett, Theodore	14-2394	3-12-cv-02121
Bowden, Gregory	14-2395	3-12-cv-02127
Kniffen, Donna	14-2396	3-12-cv-02150
Mayer, Christine	14-2397	3-12-cv-02159
Lynch, Kiersten	14-2398	3-12-cv-02210
Dunn, Lucille	14-2399	3-12-cv-02211
Nelson, Susan	14-2400	3-12-cv-02258
Lindenmeier, Janet	14-2401	3-12-cv-02265
Frye, Barbara	14-2402	3-12-cv-02302
Sandfort, Irma	14-2403	3-12-cv-02371
Odum, Connie	14-2404	3-12-cv-02451
Latta, Theresa	14-2405	3-12-cv-05581
Kirkpatrick, Judy	14-2406	3-12-cv-02559
Canaday, Connie	14-2407	3-12-cv-02560

Edwards, Donna	14-2408	3-12-cv-02561
Lackey, Karen	14-2409	3-12-cv-02594
Evans, Dorothy	14-2410	3-12-cv-02596
Brown, Towanda	14-2411	3-12-cv-02598
Tressler, Vera	14-2412	3-12-cv-02600
Heldberg, Judith	14-2413	3-12-cv-02647
Hen, Azucena	14-2414	3-12-cv-02771
Sias, Diana Van Pelt	14-2415	3-12-cv-02833
Otto, Harriet	14-2416	3-12-cv-02837
Best, Bettie	14-2417	3-12-cv-02838
Davis, Betty Saki	14-2418	3-12-cv-03017
Roberts, Margaret	14-2419	3-12-cv-03021
Goias, Geraldine	14-2420	3-12-cv-03022
Lona, Lucille	14-2421	3-12-cv-03023
McMurray, Deborah	14-2422	3-12-cv-03025
Doriott, Angelita	14-2423	3-12-cv-03026
Thieman, Donna	14-2424	3-12-cv-03027
White, Claudia	14-2425	3-12-cv-03259
Eshelman, Stephanie	14-2426	3-12-cv-03260
Grillo, Maria	14-2427	3-12-cv-03261
Stefanowski, Lucy	14-2428	3-12-cv-03286
Burghardt, Pamela	14-2429	3-13-cv-07894
Gerber, Marilyn	14-2430	3-12-cv-03326
Tong, Lucy	14-2431	3-12-cv-03328
Venner, Vida	14-2432	3-12-cv-03329
Uslan, Sharon	14-2433	3-12-cv-03330
Goldberg, Ethel	14-2434	3-12-cv-03331
Hudson, Laraine	14-2435	3-12-cv-03335
Rittenhouse, Carolyn	14-2436	3-12-cv-03345
Budd, Randal	14-2437	3-12-cv-03346
Myers, Eva	14-2438	3-12-cv-03347
Dykes, Marsha	14-2439	3-12-cv-03348
Foree, Edith	14-2440	3-12-cv-03358
Indich, Terry	14-2441	3-12-cv-3366

Travor, Lois Annette	14-2442	3-12-cv-03399
Steen, Barbara	14-2443	3-12-cv-03429
Charms, Shirley	14-2444	3-12-cv-03511
Denham, Janice	14-2445	3-12-cv-03696
Tanglao, Lourdes	14-2446	3-12-cv-03705
Disosway, Linda	14-2447	3-12-cv-03730
Lare, Sandra	14-2448	3-12-cv-03769
Nealen, Arlene	14-2449	3-12-cv-03770
DerHarootunian, Car[olyn]	14-2450	3-12-cv-03789
Yacoub, Caroline	14-2452	3-12-cv-03795
Baker, Alma	14-2453	3-12-cv-03878
Palma, Lucita	14-2454	3-12-cv-03879
Mateo, Yoshie	14-2455	3-12-cv-03904
Terranova, Patricia	14-2456	3-12-cv-03939
Hill, Mary	14-2457	2-12-cv-03959
Wilson, Selma	14-2458	3-12-cv-04014
Toland Kathleen	14-2459	3-12-cv-04190
Fillippello, Margaret	14-2460	3-12-cv-04423
Harris, Ramona	14-2461	3-12-cv-04424
Lane, Sharon	14-2462	3-12-cv-04426
Whisenant, Louise	14-2463	3-12-cv-04440
Carter, Joan	14-2464	3-12-cv-04453
Glenn, Sue	14-2465	3-12-cv-04454
Sweet, Karen	14-2466	3-12-cv-04566
Hutton, Nancy	14-2467	3-12-cv-04599
Hernandez, Antonia	14-2468	3-12-cv-04601
Favor, Judith	14-2469	3-12-cv-04604
Parker, Esther	14-2471	3-12-cv-04611
Mitchell, Cheryl	14-2472	3-12-cv-04638
Paralikis, Pamela	14-2473	3-12-cv-04656
Bottari, Donna	14-2474	3-12-cv-04663
Hedgepeth, Betty	14-2475	3-12-cv-04664
Sperber, Bernice	14-2476	3-12-cv-04721

Currie, Marlene	14-2477	3-12-cv-04760
Worthington, Jerrene	14-2478	3-12-cv-04762
Patrina, Chester []	14-2479	3-12-cv-04773
Falcone, Patricia	14-2480	3-12-cv-04802
Anselmo, Victoria	14-2481	3-12-cv-04806
Patterson, Ethel	14-2482	3-12-cv-04836
Haslam, Martha	14-2483	3-12-cv-05018
Julius, Diana	14-2484	3-12-cv-05019
Mott, Leann	14-2485	3-12-cv-05020
Theberge, Jeanne	14-2486	3-12-cv-05060
Walker, Shirley	14-2487	3-12-cv-05085
Bedsworth, Alan []	14-2488	3-12-cv-05094
Crew, Nellie	14-2489	3-12-cv-05108
Astrug, Debra	14-2490	3-12-cv-05205
Dixon, Carolyn	14-2491	3-12-cv-05269
Edgil-Rogers, Judee	14-2492	3-12-cv-05271
Gilmer, Marjorie	14-2493	3-12-cv-05297
Kovalick, Carole	14-2494	3-12-cv-05364
Knutson, Josephine	14-2495	3-12-cv-05383
Smith, Regina	14-2496	3-12-cv-05384
Hamilton-Gamman, S[andra]	14-2497	3-12-cv-05385
Needles, Josephine	14-2498	3-12-cv-05389
Kendrick, Billie	14-2499	3-12-cv-05391
Paxton, Mary	14-2500	3-12-cv-05392
Stanwood, Peggy	14-2501	3-12-cv-05393
Knopick, Carol	14-2502	3-12-cv-05485
Osburn, Gaile	14-2503	3-12-cv-05557
Miller, Dolores	14-2504	3-12-cv-05560
Heckard, Shirley	14-2505	3-12-cv-02549
Cline, Diane	14-2506	3-12-cv-05681
Cummings, Sarah	14-2507	3-12-cv-05776
Jodszuweit, Armida	14-2508	3-12-cv-05975
Collier, Nancy	14-2509	3-12-cv-05978

Sayers, Sheila	14-2510	3-12-cv-05993
Cook, Shirley	14-2511	3-12-cv-06028
Wiegand, Mary	14-2512	3-12-cv-06029
Roland, Annie	14-2513	3-12-cv-06155
Bridgeman, Max	14-2514	3-12-cv-06182
Wong, Anita	14-2515	3-12-cv-06187
Hayden, Jane	14-2516	3-12-cv-06191
McGrath, Sheila	14-2517	3-12-cv-06192
Van Blaricom, Betty	14-2518	3-12-cv-06216
Thomas, Eugune Mid[dleton]	14-2519	3-12-cv-06237
Fuerstnau, Barbara	14-2520	3-12-cv-06264
Halfmann, Mary	14-2521	3-12-cv-06266
Kimizuka, Yoshie	14-2522	3-12-cv-06267
Hofmann, Kathleen	14-2523	3-12-cv-06269
Duggan, Doris	14-2524	3-12-cv-06275
Andorka-Aceves, Deb[orah]	14-2525	3-12-cv-06289
Herndon, Lucy Mae	14-2526	3-12-cv-06301
Delikat, Ellen	14-2527	3-12-cv-06351
Mouser, Donna	14-2528	3-12-cv-06365
Hulsman, Elaine	14-2529	3-12-cv-06366
Kempfer, Faye	14-2530	3-12-cv-06376
Lotter, Dolores	14-2531	3-12-cv-06377
Cummings, Irene Lilli[an]	14-2532	3-12-cv-06378
Irving, Zepher	14-2533	3-12-cv-06397
Marcus, Rita	14-2534	3-12-cv-06430
Halpern, Marion	14-2535	3-12-cv-06432
Ogle, Ann	14-2536	3-12-cv-06433
Bittner, Marcella	14-2537	3-12-cv-06434
Wade, Kay	14-2538	3-12-cv-06437
Ahern, Frances	14-2539	3-12-cv-06439
Boshell, Marsha	14-2540	3-12-cv-06443

Sandt, Faye	14-2541	3-12-cv-06444
Holmes, Leanne	14-2542	3-12-cv-06445
Napoli, Anna	14-2543	3-12-cv-06446
Vaughn, Patricia	14-2544	3-12-cv-06450
Irizarry, Sheila	14-2545	3-12-cv-06451
Kort, Barbara	14-2546	3-12-cv-06453
Kosvick, Melinda	14-2547	3-12-cv-06454
Homa, Barbara	14-2548	3-12-cv-06455
Stepanski, Mary Jo	14-2549	3-12-cv-06456
Lare, Barbara	14-2550	3-12-cv-06457
Nguyen, Susan	14-2551	3-12-cv-06458
Jeet, Lalita	14-2552	3-12-cv-06459
Naik, Khadijah	14-2553	3-12-cv-06460
Bartlett, Ann	14-2554	3-12-cv-06461
Aydin, Jean	14-2555	3-12-cv-06462
Dowd, Jeanette	14-2556	3-12-cv-06463
Van Gosen, Helen	14-2557	3-12-cv-06464
Huddleston, Shirley	14-2558	3-12-cv-06465
Griffin, Jennifer	14-2559	3-12-cv-06466
Crisci, Stephen N. []	14-2560	3-12-cv-06469
Jones, Geraldine	14-2561	3-12-cv-06550
McKinney, Carlene	14-2562	3-12-cv-06711
Karantza, John	14-2563	3-12-cv-06719
Bozue, Dorothy	14-2564	3-12-cv-06770
Cline, Beatrice	14-2565	3-12-cv-06840
Broadstone, Judith	14-2566	3-12-cv-06841
Schmitt, Luise Gerlin[de]	14-2567	3-12-cv-06845
Cherco, Patricia	14-2568	3-12-cv-06846
Neuman, Janet	14-2569	3-12-cv-06850
Isom, Leann	14-2570	3-12-cv-06859
Heiny, Joyce	14-2571	3-12-cv-06860
Vertuccio, Lana	14-2572	3-12-cv-06863
Williams, Susanne	14-2573	3-12-cv-06877

Stevenson, Nada	14-2574	3-12-cv-06899
Elison, Linda	14-2575	3-12-cv-06900
Lingo, Melba	14-2576	3-12-cv-06901
Baylor, Richard	14-2577	3-12-cv-06903
Thompson, Loralee	14-2578	3-12-cv-06905
Miller, Esther	14-2579	3-12-cv-06907
Orr, June	14-2580	3-12-cv-06952
Maki, Gale	14-2581	3-12-cv-06954
Collins, John	14-2582	3-12-cv-06955
McAnulty, Joan	14-2583	3-12-cv-06956
Abney, Virginia	14-2584	3-12-cv-06957
Altson, Amy	14-2585	3-12-cv-07023
Harris, Hope []	14-2586	3-12-cv-07048
Jaeger, Bernadette	14-2587	3-12-cv-07443
Couture, Diane	14-2588	3-12-cv-07819
VanDyke, Patricia	14-2589	3-13-cv-00001
Antoff, Christine	14-2590	3-13-cv-00137
Wyly, Lois Ann	14-2592	3-13-cv-00171
Conner, Cheryl	14-2593	3-13-cv-00442
Kardon, Koula	14-2594	3-13-cv-00718
Bialkowski, Mary	14-2595	3-13-cv-00720
Affronti, Joanne	14-2599	3-13-cv-00816
Bannon, Gladys	14-2600	3-13-cv-00818
Golden, Jane	14-2601	3-13-cv-00894
Pitts, Shirley Ann	14-2602	3-13-cv-00926
Slinkman, William Ric[hard]	14-2603	3-13-cv-00928
Albert, Elizabeth	14-2604	3-13-cv-01062
Hawk, Joycelyn	14-2605	3-13-cv-01063
Pritchard, Helen	14-2606	3-13-cv-01071
Myers, Susan	14-2607	3-13-cv-01215
Brooks, Betty	14-2608	3-13-cv-01314
Hawkins, Amy	14-2609	3-13-cv-01337
Edmondson, Maxine	14-2610	3-13-cv-01340

Kamienski, Mary	14-2611	3-13-cv-01352
Neuman. Delores	14-2612	3-13-cv-01369
Peters. Alohoa	14-2613	3-13-cv-01370
Routhieaux, Marguer[itte]	14-2614	3-13-cv-01371
Alberg, Evelyn	14-2615	3-13-cv-01378
Goodman, Carol Ann	14-2616	3-13-cv-01415
Samuelson. Johann	14-2618	3-13-cv-01476
Rudolph. Joyce	14-2619	3-13-cv-01884
Romeo. Alice	14-2620	3-13-cv-02616
Grems. Mary	14-2621	3-13-cv-02617
McKeon-Cincotta, Le[na]	14-2622	3-13-cv-02649
Jernigan, Mary Lou	14-2623	3-13-cv-02735
Wicker, Marie	14-2624	3-13-cv-02827
Stampliakis. Helen	14-2625	3-13-cv-02836
Crook, Judith	14-2626	3-13-cv-02958
London, Phyllis	14-2627	3-13-cv-03211
Connor. Ruth	14-2628	3-13-cv-03353
Mulqueen. Mary	14-2629	3-13-cv-03353
Bergmann, Ruth	14-2630	3-13-cv-03474
Spallone, Josephine	14-2631	3-13-cv-03741
Maddern, Karen	14-2632	3-13-cv-03929
Marcelles, Sara	14-2634	3-13-cv-04075
Tolston. Betty	14-2635	3-13-cv-05984
Oakes, Miriam	14-2636	3-11-cv-06090
Murphy, Nancy	14-2813	3-12-cv-05082
Montgomery, Rulene	14-3220	3-12-cv-06282
Gaynor, Barbara	14-3267	3-12-cv-01492

APPENDIX C

United States District Court, D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM): PRODUCTS LIABILITY LITIGATION.
This Document Relates to: All Actions.

MDL No. 2243.
|
Master Docket No. 08–08(JAP)(LHG).
|
Signed March 26, 2014.

OPINION

PISANO, District Judge.

This matter is presently before the Court on an Order to Show Cause ("OTSC") issued on August 15, 2013 [docket # 2895], directing the Plaintiffs listed in Appendix A of the Order (collectively referred to as "Plaintiffs"), to show cause why their pre-September 14, 2010, injury claims should not be dismissed on preemption grounds pursuant to this Court's ruling in the Bellwether *Glynn* case. *See Glynn v. Merck Sharp & Dohme, Corp.*, Case Nos. 11–503, 08–08, —— F.Supp.2d ——, 2013 WL 3270387 (D.N.J. Jun.27, 2013).

In response to the OTSC, the Court received the following briefs from Plaintiffs: (1) Plaintiff Deborah Thompson's Response to the OTSC [docket # 2931]; (2) Plaintiff Helen Stampliakas's Response to the OTSC [docket # 2932]; (3) Plaintiff Elaine Howe's Response to the OTSC [docket # 17 on 11–6657](4) Plaintiffs' Adverse Reactions and Long–Term–Use Failure–to–Warn Brief ("Adverse Reactions Brief") [docket # 2995(1)]; (5) Plaintiffs' DesignDefect and Other Non Failure to Warn Claims Brief ("Design Defect Brief") [docket # 2995(2)]; (6) Plaintiffs' Procedural Brief [docket # 2995(3)]; and (7) Plaintiffs' Warnings and Precautions Brief [docket # 2995(4)].

Merck replied to Plaintiffs' response to the OTSC and filed the following briefs in support of its position: (1) Reply to Plaintiff Helen Stampliakas's and Plaintiff Deborah Thompson's Responses to the Court's OTSC [docket # 3030]; (2) Reply to Plaintiff Elaine Howe's Response to the Court's OTSC [docket # 3041] (3) Reply to Plaintiffs' Adverse Reactions and Long–Term–Use Failure–to–Warn Brief ("Merck's Adverse Reactions Brief") [docket # 3031]; (4) Reply to Plaintiffs' Design Defect and Other Non–Failure to Warn Claims Brief ("Merck's Design Defect Brief") [docket # 3031(1)]; (5) Reply to Plaintiffs' Procedural Brief [docket # 3031(3)]; and (6) Reply to Plaintiffs' Warnings and Precautions Failure to Warn Brief [docket # 3031(2)].

By way of brief background, Plaintiffs brought this lawsuit against Merck, the manufacturer of Fosamax, which is a drug approved by the United States Food and Drug Administration ("FDA") for the treatment

and prevention of osteoporosis. This matter is part of the multi-district litigation ("MDL") concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("A FFs[1]"), it caused Plaintiffs' injuries, and Defendant failed to warn physicians about Fosamax causing AFFs. For the reasons set forth below, Plaintiffs' have failed to show cause why their pre-September 14, 2010, injury claims should not be dismissed on preemption grounds. Preemption was dispositive of *Glynn* and cuts across all pre-label change cases. Accordingly, Defendant is entitled to judgment as a matter of law on the Appendix A Plaintiffs' claims.

I. OVERALL PROCEDURAL HISTORY

In May 2011, the Judicial Panel on Multidistrict Litigation centralized in this Court a number of related actions brought by patients who suffered femur fractures or similar bone injuries after taking Fosamax [docket # 30]. On July 14, 2011, the Court ordered a process for selection of three or four Early Trial Cases and directed a schedule for expert discovery [docket # 113]. On November 14, 2012, the Court designated trial dates for the four Early Trial Cases, with the earliest, *Glynn*, set for April 8, 2013 [docket # 1915]. General fact discovery closed on December 31, 2012, pursuant to Case Management Order No. 10 [docket # 848].

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[1] The abbreviation of atypical femur fracture (singular) is "AFF."

On January 15, 2013, Merck moved for summary judgment in *Glynn* on federal preemption grounds, arguing that the Plaintiffs' claims were preempted because the FDA's rejection of Merck's proposed Precaution disclosing a risk of low-energy femoral shaft fracture from Fosamax use made it impossible for Merck to warn the Plaintiffs' of that risk [docket # 25 in 11–5304]. This Court heard oral argument on the federal preemption issue on March 8, 2013, and reserved decision until a trial record had been established. A jury trial took place in *Glynn* from April 8, 2013 to April 29, 2013. The parties then briefed the preemption issue three more times: a Rule 50(a) motion for judgment as a matter of law at the close of Plaintiffs' case [docket # 198 in 11–5304]; a renewed Rule 50(a) motion at the close of all evidence [docket # 209 in 11–5304]; and a Rule 50(b) renewed motion for judgment as a matter of law [docket # 216 in 11–5304].

On June 27, 2013, after considering all of the parties briefing, evidence, arguments, and the trial record, the Court granted Merck's motion(s) and found that Plaintiff's state law claim for failure to warn was preempted because clear evidence existed that the FDA would not have approved a stronger warning to the Fosamax label as of the date of Ms. *Glynn*'s injury. *Glynn*, 2013 WL 3270387, at * 1. On August 1, 2013, Merck then moved for an OTSC why the claims of all other Plaintiffs with injury dates prior to September 14, 2010, should not be dismissed pursuant to the Court's preemption ruling in *Glynn* [docket # 2857]. On August 5, 2013, Plaintiffs' submitted a letter brief opposing the entry of an OTSC [docket # 2870], and Merck replied by letter on

August 12, 2013 [docket # 2881]. The Court, observing that it had "afford[ed] the Plaintiffs' Steering Committee ... and *Glynn*'s counsel repeated opportunities to present their evidence" and that the *Glynn* ruling turned on issues common to all Plaintiffs, granted Merck's motion on August 15, 2013 [docket # 2895].

As stated above, the parties submitted several briefs and filings in support of their responses to the OTSC. The Court will address each argument separately below.

II. BACKGROUND

A. History of the Fosamax Label Change

In September 1995, the FDA approved Fosamax for the treatment of osteoporosis in postmenopausal women, and in April 1997, the FDA approved Fosamax for the prevention of osteoporosis in postmenopausal women. Since this time, Fosamax has remained FDA approved for the treatment and prevention of postmenopausal osteoporosis. On June 13, 2008, the FDA contacted Defendant and other bisphosphonate[2] manufacturers and requested any investigations they conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational plans, and "all hip and femoral fracture case reports" they received [docket # 3032, *Merck's Preliminary Statement of Facts Relating to the Court's Order to Show Cause*

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[2] Fosamax belongs to a class of drugs known as bisphosphonates.

("Merck's Statement of Facts") ¶ 28]. The FDA also asked that Defendant and the other bisphosphonate manufacturers make an effort where possible "to clarify the fracture location and the duration of bisphosphonate exposure for all case reports." *Id.* at ¶ 44. The FDA explained that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and was "concerned about this developing safety signal." *Id.* at ¶ 43.

On July 18, 2008, Defendant responded to the FDA's request and included summary tables of clinical and post-marketing data, clinical Council for International Organizations of Medical Sciences ("CIOMS") reports, and post-marketing CIOMS reports. *Id.* at ¶ 47. The FDA's review of this data as well as the data from other bisphosphonate manufacturers "did not show an increase in ... [the risk of atypical subtrochanteric femur fractures] in women using these medications." [docket # 3035, *Declaration of Karen A Confoy in Support of Merck's Replies to Plaintiffs' Briefs in Response to Court's Order to Show Cause and in Support of Merck's Preliminary Statement of Facts* ("Confoy Dec."), Ex. 73].

On September 15, 2008, Defendant submitted a Prior Approval Supplement ("PAS") to the FDA, proposing "to add language to both the Precaution[s] and Adverse Reactions/PostMarketing Experience section[s] of the label to describe low-energy" subtrochanteric femoral fractures. Merck's Statement of Facts, ¶ 73. Defendant explained that "[i]t is not possible with the present data to establish

whether treatment with" Fosamax "increases the risk of [these] ... low-energy subtrochanteric and/or proximal shaft fractures," but because there is a temporal association between these fractures and Fosamax, Defendant thought that it was "important to include an appropriate statement about them in the product label." *Id.* Defendant sought to add the following language to the Precautions section of the label:

> Low–Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonatetreated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e .g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation

> of the patient, based on individual benefit/risk assessment.
>
> [*Id.* at ¶ 74].

Additionally, Defendant proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions/Post–Marketing Experience section of the label and the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh." *Id.*

On April 15, 2009, an FDA representative e-mailed Defendant and stated that the label change to the Adverse Reactions/Post–Marketing Experience section of the label would be approved but the label change to the Precautions section would not be approved. *Id.* at ¶ 79. On May 22, 2009, the FDA formally responded to Defendant's proposed label change, recommending that it add "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions/Post–Marketing Experience section of the label; however, the FDA still did not approve the label change to the Precautions section. *Id.* at ¶ 80. Moreover, the FDA warned that Fosamax "may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if [it is] ... marketed with" these label changes "before [FDA] approval...." *Id.*

On July 2, 2009, Defendant submitted to the FDA a Changes Being Effected ("CBE") supplement to add the FDA's proposed language about femur fractures to the Adverse Reactions/Post–Marketing Experience section of the label, which was later approved. *Id.* at

81. On March 10, 2010, the FDA issued a Drug Safety Communication, in which it stated that "[a]t this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" *Merck's Statement of Facts*, $ 85. The FDA did state, however, that it was "working closely with outside experts, including members of the ... American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue." *Id.*

On September 14, 2010, the American Society for Bone and Mineral Research ("ASBMR") published an article entitled *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. Id* . at ¶ 86. The report stated that although there is an association between long-term bisphosphonate use and A FFs, the association had not been proven to be causal. *Id.* The FDA responded to the report by issuing a Drug Safety Communication, in which it stated "[a]lthough it is not clear if bisphosphonates are the cause [of AFFs], these unusual femur fractures have been identified in patients taking these drugs." *Id.* at $ 87. Regarding the ASBMR Task Force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports ..." and would be "considering label revisions." *Id.* (emphasis added).

In October 2010, the FDA issued another Drug Safety Communication, informing that it would require all bisphosphonate manufacturers to add information on AFFs to the Precautions section of the drug labels and require a new Limitations of Use statement in the Indications and Usage section of the label because "these atypical fractures may be related to long-term ... bisphosphonate use." *Id.* at ¶¶ 88–89. It reiterated that it was still "not clear if bisphosphonates are the cause," but noted that these "unusual femur fractures" may be related to long-term bisphosphonate use. *Id.* at $ 88. The FDA's proposed labeling language noted that "[c]ausality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates." *Id.* at ¶ 89. On January 11, 2011, Defendant submitted the agreed upon label changes to the FDA. *Id.*

Currently, the Fosamax label includes the following language: "Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients.... Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area." [docket # 2996, *Declaration of Donald A. Ecklund* ("Ecklund Dec."), Ex. 9].

B. *Glynn* Ruling

As noted above, before the Court in *Glynn* were several motions by Defendant[3] , all of which were premised on federal preemption. The issue in these motions was whether clear evidence existed that the FDA would not have approved a stronger warning to the Fosamax label, thereby warranting preemption of the *Glynn* Plaintiffs' failure to warn claim. *See Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). This Court heard oral argument on the preemption issue on March 8, 2013, and reserved decision until a trial record had been established. *See* Fed.R.Civ.P. 78. A jury trial took place from April 8, 2013 to April 29, 2013, and the jury returned a verdict for Defendant, finding that Plaintiff *Glynn* did not prove that she experienced an AFF in April 2009 by a preponderance of the evidence.

On the day following the conclusion of the trial, the Court held an in-person status conference where it discussed the preemption issue and gave the Plaintiffs twenty-one (21) days to submit "proposed fact findings that [were] based upon the record in opposition to" the preemption motions. [docket # 250

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[3] The motions before the Court in *Glynn* were: (1) Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25 in 11–5304]; (2) Defendant's Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 198 in 11–5304]; (3) Defendant's Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 209 in 11–5304]; and (4) Defendant's Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216 in 11–5304].

in 11–5304, *Hearing Tr.*, 19:24–20:1; April 30, 2013]. Thereafter, on May 6, 2013, Defendant submitted its Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216 in 11–5304], arguing that the *Glynn* Plaintiffs' claims were preempted because Defendant submitted to the FDA all of the information relevant to a label change and tried to change the Precautions section of the label to include low-energy femoral fractures, but the FDA rejected this change. The Court agreed with Merck's position and on June 27, 2013, granted Defendant's motion(s). *See* Generally *Glynn*, 2013 WL 3270387.

C. Arriving at the OTSC

With the history of *Glynn* as a backdrop, it is necessary to address the evolution of the preemption issue, how the case has gotten to the point of having an OTSC on the issue, and the fact that the parties have been aware of the potential global effects preemption could have on the entire MDL for at least two (2) years. Throughout the entire pre-trial, trial, and post-trial proceedings in *Glynn*, the Court made it clear that, prior to ruling on preemption, it wanted the parties to introduce any and all relevant evidence to the issue because of the effects it could have on the MDL as a whole. During this time—even prior to any motions being filed by Defendant—Plaintiffs' were aware of the exact position that Merck took surrounding preemption, how Merck planned to raise this argument, and the fact that Merck believed preemption likely hinged on the date of a Plaintiff's injury.

Indeed, before Ms. *Glynn* was even selected as the Bellwether case for trial, the parties appeared before

the Court on May 14, 2012, where counsel for Merck reiterated the fact that the date of injury was central to the analysis and advised the Court and Plaintiffs of Defendant's position on preemption. [docket # 1397, *Hearing Tr.*, 13:25–14:2; 14:12–14:14; 15:16–15:19; 22:5–22:7; May 14, 2012 ("MR. MARSHALL: ... I want to focus in on some of the labeling issues because they're going to be very important in the case ... [it's] going to be a very important point in these cases because we will be raising a preemption argument ... [t]hat defense will be raised as a substantive legal motion ... [and] it will be based upon when the injury occurred ... [a] key factor ... is the timing of the injury....")]. Stated differently, for almost an entire year prior to the *Glynn* trial, Plaintiffs were aware of Defendant's position on preemption, the fact that it would be raised by way of substantive motion and that such motion would be directly related to the timing of injury. Fact discovery closed seven (7) months thereafter and the preemption issue was then briefed four separate times.

As the *Glynn* trial moved closer, the parties were advised of the Court's desire to have any and all arguments and evidence relevant to preemption on the record. [docket # 244 in 11–5304, *Trial Tr., Vol. 9*, 1885:7–1885:12; April 22, 2013 ("THE COURT: ... I have indicated my intention to ultimately rule on that [preemption] motion after I've had the benefit of a complete trial record ... I think I'm correct that a full trial record would benefit me and both sides before a ruling is made.")]. Further, after the close of Plaintiff's case in the *Glynn* trial, Plaintiffs were *again* made aware of the exact position Merck took

with respect to the evidence set forth and the issues Merck planned to *again* raise surrounding preemption. *Id.* at 1908:12— 1908:17 ("MR. MARSHALL: ... The FDA had in its possession all of the information that plaintiffs now rely upon to say that a label change could be made. We tried to do it, it was rejected. We are precluded, prevented from doing it. That, your Honor, is the preemption argument."). Despite Merck's contention that no dispute of fact existed for the jury to decide, the Court continued to reserve its decision on the preemption motion(s) to ensure a full trial record was established with all evidence relevant to the issue.

Immediately following the trial on April 30, 2013, the parties appeared before the Court to discuss the process of moving the MDL forward and, again, the Court reiterated that it has been urging Plaintiffs to come forward with *any and all evidence* on the preemption issue, as the parties all agreed that it would have widespread implications on the M DL as a whole:

> *MR SEEGER:* ... **I'm thinking that the preemption issue because it's going to cut across all 3,000 cases. Pretty much if it goes the wrong way for plaintiffs, it's pretty much the end of the litigation.**
>
> ...
>
> *THE COURT*: There have been three iterations of the preemption motion and **my position all along was to make f that I wanted to be sure, first of all, that I had a complete record from which to decide the preemption issue**. And I thought the best way to do that was to try the *Glynn* case,

because that was the case that was coming in, knowing that there was going to be **evidence introduced which would bear upon Merck's conduct with the FDA and whether there would be clear evidence that [the] FDA would not have permitted the label change**, which is what Merck has to show under *Wyeth v. Levine*.

...

I don't know what more you want to put in the record. **I invited you, I invited the plaintiffs and I was urging the plaintiffs to put in what there could be bearing on the question.** I don't know what else there is.

...

The issue in the case is whether there's anything in the regulatory record from which the Court would conclude that it's clear the FDA would not have permitted the label change. Now, the label change was an issue in the *Glynn* case. It was an issue in the *Glynn* case that was addressed by Dr. Blume, it was addressed by Dr. Madigan and it certainly was addressed by Dr. Santora and Daifotis.

I'm not so sure there's anything else and if there was something else, I have been begging for it.

...

... **It was clear to me and everybody else that there was substantial consequences to this motion. We've had a hundred conversations, all of us, since then where I have been saying the same thing, namely, that I wanted-that it was**

important to decide this case, this issue one way or another so that there could be some appellate review and we get a sense of it, because we know we're holding 3300 cases hostage.

[docket # 250 in 11–5304, *Hearing Tr.*, 5:10–5:13; 6:10– 6:19; 7:13–7:17; 16:6–16:14; 18:15–18:21; April 30, 2013 (emphasis supplied)].

Similarly, after the Court granted Merck's preemption motion(s) in *Glynn*, the parties appeared before the Court on July 18, 2013, to again address, among other things, how the preemption issue would be treated going forward and the fact that preemption would cut across all of the cases in the MD L:

> *THE COURT:* I think it's an accurate statement, Mr. Morris, that **I have been consistent in asking the plaintiffs to come forward with any evidence that would bear upon that preemption decision and I didn't decide it until I was satisfied that there had been a full opportunity to be heard on the question and the opinion stands for itself.**
>
> ...
>
> This business about all the plaintiffs having their own claims and their own injuries and their own doctors is all very well and fine and that's true, **but the focus from the preemption issue, the focus is more on Merck than on the plaintiffs.**
>
> *THE COURT:* ... [W]hat I would expect then is there to be some sort of an effort by Merck to close the door on these cases.

MR. MORRIS: **Right, we expected that ...**

[docket # 2998, *Hearing Tr.*, 10:3–10:8; 10:16–10:20; 11:8–11:10; July 18, 2013 (emphasis supplied)].

As a review of the record reveals, the preemption issue has existed since this MDL's inception and preemption has almost certainly been the forefront of the litigation for the past two (2) years. It has never been a secret as to what Merck's position is with respect to preemption, and Plaintiffs have long been aware that their case(s) may depend entirely on the date of injury. Further, as referenced above, for the past two (2) years the parties and the Court have been operating under the common understanding that this Court's decision on preemption could impact the entire MDL. Stated differently, Plaintiffs and Defendant knew that while the motions before the Court in *Glynn* were specific to the date of Ms. *Glynn*'s injury, the Court's decision on such motions would almost certainly have an effect on a substantial amount of Plaintiffs other than Ms. *Glynn*. Thus, the Court purposely reserved deciding the issue to ensure that *any and all facts relevant to preemption* would appear on the record. In doing so, the Court repeatedly urged Plaintiffs to come forward with all evidence bearing on preemption, allowed the parties several opportunities to brief the issue, entertained oral argument on the motion(s), conducted an entire trial which invited any evidence relevant to preemption, and addressed the issue at various hearings. Then, after finally ruling on preemption in *Glynn*, the Court issued an OTSC—giving the parties yet another opportunity to brief the issue—to address what has *long* been known as a

predominant issue in the case: namely, what effect does the Court's preemption ruling have on the other Plaintiffs whose injuries occurred prior to the date of the label change?

III. DISCUSSION

A. Procedural Arguments

The parties each submitted briefing on the procedural aspects of the Court's OTSC in the context of an MDL. Plaintiffs' and Defendant concede that Rule 56 provides the proper standard for the Court's analysis here; however, the parties disagree over the burden shifting, as well as the Court's ability to utilize an OTSC to apply the *Glynn* ruling to other Plaintiffs. This Court agrees with the parties' contention that Rule 56 provides the exclusive mechanism by which the Court can resolve the dispositive issues presented by Merck's preemption defense before trial(s).

i. Procedural Analysis

The Court must first address the proper standard to be applied pursuant to Rule 56 as well as where the appropriate burden lies in this OTSC context. Under Rule 56, summary judgment is applicable when the Court is satisfied that there is no genuine issue of material fact and the evidence establishes the moving party's entitlement to judgment as a matter of law. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323, 106 S.Ct. 2548, 2553, 91 L.Ed.2d 265 (1986). "If the moving party meets the initial burden of establishing that there is no genuine issue, the burden shifts to the nonmoving party to produce

evidence of a genuine issue for trial." *Degrange v. W.*, 196 F. App'x 91, 93 (3d Cir.2006).

This Court agrees with Merck's contention that Defendant's initial burden pursuant to Rule 56 has already been met by way of the briefing in *Glynn*. As stated above, Merck briefed the preemption issue four (4) separate times and in doing so, met its burden of establishing that there is no genuine issue(s) of fact with respect to preemption. This is further evidenced by the Court's judgment as a matter of law in favor of Merck, holding that clear evidence exists that the FDA would not have approved a stronger warning prior to the date of Ms. *Glynn*'s injury.[4] *See* Generally *Glynn*, 2013 WL

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[4] It should be noted, however, that despite the *Glynn* ruling being specific to Ms. *Glynn* and the date of her injury, Merck's briefing in *Glynn* is still relevant to all Plaintiffs' identified in this Court's OTSC because the briefs in *Glynn* centered generally on *when* clear evidence existed that the FDA would not have approved a label change. *See Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of Motion for Summary Judgment Based upon Federal Preemption*, p. 18 [docket # 25 in 11–5304] ("... [I]t was not until the ASBMR report was issued in September 2010, reporting that bisphosphonates, when used long-term, may be related to femoral fractures, that the FDA determined available scientific evidence supported a Precaution."); *Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of its Motion for Judgment as a Matter of Law*, p. 2, 18 [docket # 198 in 11–5304] and *Defendant Merck Sharp & Dohme Corp.'s Memorandum of Law in Support of its Renewed Motion for Judgment as a Matter of Law*, p. 1, 12 [docket # 209 in 11–5304] ("[Plaintiff's] claims would be preempted because Merck proposed ... such a Precaution and the FDA rejected it ... such a rejection is "clear evidence" that the FDA would have

3270387. Thus, Merck has demonstrated the absence of any genuine issue of material fact surrounding preemption and the burden is therefore shifted to Plaintiffs to produce a genuine issue for trial by way of their briefing in response to the Court's OTSC.

Plaintiffs' assert that they have met this burden because subsequent to the *Glynn* ruling, there have been additional documents exchanged and additional expert testimony which creates a genuine issue of fact as to what Merck could have or should have done in connection with updating its label.[5] However, what

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rejected any warning about fractures ..." and "Dr. Blume testified clearly and repeatedly ... that a pharmaceutical company's duty to change its label to warn of an adverse event does not arise until there is 'reasonable evidence of a causal association' under 21 C.F.R. § 201.57"); *Merck Sharp & Dohme Corp.'s Reply in Support of Rule 50(B) Motion for Judgment as a Matter of Law*, pp. 5–6 [docket # 230 in 11–5304] ("Simply put: the change in the FDA's approach between 2008 and 2010 did not result from a change in FDA policy with respect to line-editing proposed warnings ... Rather, it resulted from an evolution in the FDA's views about the science relating to atypical femur fractures, which did not crystallize until late 2010.").

[5] Plaintiffs' claim that "new evidence" presently before the Court includes Ex. 161 to the *Declaration of Donald A. Ecklund*, which was a statement from the FDA in December, 2010 about why it was rejecting the label change and that because the FDA struck out the term "stress fracture," this Court cannot find that clear evidence exists that the FDA would have rejected a label change that did not use the "stress fracture" language. However, it should be noted that the December, 2010 statement from the FDA was before the Court in *Glynn* and therefore, this is not "new evidence" that the Court has not already considered in determining that no material fact dispute exists. *See Declaration of Edward*

Merck *could have* or *should have* done is immaterial because we know what Merck *did*. Similarly, ***Wyeth v. Levine*** provides for preemption where there is clear evidence that the FDA *would have* rejected a label change, and again, we know that the FDA *did* reject it. Thus, any expert testimony relating to what Merck *could have* or *should have* done, and what the FDA *would have* done in response to the same, is purely speculation and does not rise to the level of being a genuine fact dispute. Allowing Plaintiffs the opportunity to present individual expert testimony would also defeat the efficiency of an MDL because Plaintiffs would go through expert after expert, and none of the testimony would change what actually transpired between Merck and the FDA.

Further, the Court disagrees with Plaintiffs' contention that their Seventh Amendment rights and the procedural protections safeguarded in Rule 56 are being circumvented. Plaintiffs' suggest that the preemption determination must be made by a fact finder; however, if this were the case, the Court's preemption ruling in *Glynn* would be improper.[6] This assertion is not convincing. Rather, as evidenced by the cases cited to by Plaintiffs, where there is *no factual dispute* surrounding a preemption determination, summary judgment is proper. *See Boyle v. United Technologies Corp.*, 487 U.S. 500, 501, 108 S.Ct. 2510, 2513, 101 L.Ed.2d 442 (1988) ("If

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Braniff in Support of Plaintiff's Opposition to Defendant's Motion for Judgment as a Matter of Law, at Ex. 1 [docket # 199 to 11–5304].

[6] It should be noted that Plaintiff *Glynn* did not appeal this Court's June 27, 2013, Order on preemption.

the evidence presented in the first trial would not suffice, as a matter of law, to support a jury verdict under the properly formulated [preemption] defense, *judgment could properly be entered for respondent at once*, without a new trial. It is unclear from the Court[s] of Appeals' opinion, however, whether it was in fact *deciding that no reasonable jury could*, under the properly formulated [preemption] defense, have found the petitioner on the facts presented, or rather was assessing on its own whether the defense had been established. *The latter would be error*, since whether the facts established the conditions for the [preemption] defense is a question for the jury." (emphasis supplied)); *Brown v. Earthboard Sports USA, Inc.*, 481 F.3d 901, 913 (6th Ci r.2007) ("*Should the movants fail to meet their burden* ... such as *if a genuine issue of material fact exists* regarding the claim's actual qualification for federal preemption, the matter must be determined by the factfinder." (emphasis supplied)).

Plaintiffs' procedural protections and Seventh Amendment argument is no more than a reiteration of the summary judgment standard. As the Court has already stated, Merck met its burden of proving that no there is no genuine issue of fact surrounding preemption by way of the briefing and trial record developed in *Glynn*. As a result, Plaintiffs are being afforded the procedural protections of Rule 56, and this Court is neither violating their Seventh Amendment rights nor "deciding factual disputes." Were the Court to determine that there *is* a genuine dispute of fact, it would deny summary judgment; however, in determining that there *is no factual*

dispute, the Court is not thereby "deciding factual disputes."

Moreover, utilizing an OTSC to apply a prior legal ruling to other Plaintiffs in an M D L is hardly inappropriate as suggested by Plaintiffs. Rather, several M DL courts have used an OTSC to do just that. *See In re Darvocet, Darvon & Propoxyphene Products Liab. Litig.*, 2012 WL 3290145, at * 1 and fn. 1 (E.D.Ky. Aug. 10, 2012) ("Here, the Court has previously determined that product liability claims against Generic Defendants are preempted ... [The Show Cause Order] directed all plaintiffs with claims against any Generic Defendant to show cause why those claims should not be dismissed pursuant to the Court's Memorandum Opinion and Order Regarding Generic Defendants' Motions to Dismiss."); *In re Allstate Ins. Co. Fair Labor Standards Act Litig.*, 2009 WL 3011042, at * 1 (D.Ariz. Sept.16, 2009) ("[I]n this MDL action ... summary judgment would be granted in the defendants' favor as to all claims of any Continuing Plaintiff who did not show cause in writing ... explaining why the Court's reasoning in the summary judgment order ... which the Court entered in the ... member case, should not be applied to him or her."); *In re Sulzer Hip Prosthesis & Knee Prosthesis Liab. Litig.*, 455 F.Supp.2d 709, 712–13 (N.D.Ohio 2006) ("In *Moore*, Sulzer moved for summary judgment on the ground that all of Moore's claims were preempted by federal law ... In light of the Court's conclusion in *Moore*, Sulzer moved the Court to issue an Order requiring all similarly-situated plaintiffs ... to show cause why their cases should not also be dismissed. The Court acquiesced to this request."). In doing so, the Court is not

applying a *factual* determination made in *Glynn* to the Plaintiffs identified in the OTSC, but a *legal* determination: namely, that there is clear evidence the FDA would have rejected a stronger Fosamax warning label, thereby preempting Plaintiffs' claims.

Further, the OTSC does not give an impermissible preclusive effect to the *Glynn* ruling because the Court is not automatically applying the holding in *Glynn* to other Plaintiffs. Instead, despite having been aware of the preemption issue for two (2) years, briefing the issue four (4) separate times, and conducting an entire trial whereby any evidence relevant to preemption could be introduced, the OTSC provides affected Plaintiffs *another* opportunity to identify genuine issues of material fact that would preclude summary judgment on their claims. Plaintiffs' failure to meet their burden pursuant to Rule 56 does not then equate to issue and/or claim preclusion. Plaintiffs' contention that further factual and expert discovery should be afforded these Plaintiffs, and that each MD L Plaintiff is entitled to litigate the preemption issue, is similarly misguided. The Court has repeatedly advised Plaintiffs' counsel to come forward with any and all evidence surrounding preemption; thus, the failure to properly gather factual and expert discovery prior to this OTSC is no fault other than Plaintiffs. Additionally, in making these discovery related arguments, Plaintiffs are improperly focusing on the relationship between the *individual Plaintiffs* and *Merck*; however, as the Court has explicitly stated on the record, the preemption analysis is entirely dependent on the relationship between *Merck* and the *FDA*.

The Court is not convinced that, whether clear evidence exists that the FDA would have rejected a stronger warning label to Fosamax, has any relevance to the individual Plaintiff and his or her potential factual differences. Rather, the material fact relevant to the preemption determination and the OTSC does not differ amongst the Plaintiffs listed in Appendix A—an injury that occurred prior to September 14, 2010. Plaintiffs have failed to show how uncovering additional information on behalf of each individual Plaintiff would change the analysis or preclude summary judgment here and therefore an extension of discovery is not warranted. *See Penn. Dep't of Pub. Welfare v. Sebelius*, 674 F.3d 139, 157 (3d Cir.2012). Further, while the Court is sympathetic to the Plaintiffs and their respective injuries, to give each of the Plaintiffs identified in the Courts OTSC their "own day in court" to litigate a legal issue that has already been conclusively determined would not only be a waste of judicial resources but would be contradictory to the premise of pre-trial motions and summary judgment. While Ms. *Glynn* had her "day in court," such was for the purpose of developing a complete trial record on the preemption issue; however, the Court need not have several hundred trial records, with the same evidence, to decide the very same issue.

As Merck correctly points out, this case is distinguishable from *In re TMI Litig.*, 193 F.3d 613 (3d Ci r.1999) *amended*, 199 F.3d 158 (3d Ci r.2000) because there, the Third Circuit concluded that the District Court "could not properly extinguish the substantive rights of the 1,900 Non–Trial Plaintiffs *merely because* all of the cases had been consolidated

... because the Non–Trial Plaintiffs were not even litigating their claims and not presenting arguments to the District Court." *Id.* at 725 (emphasis supplied). Here, the Court is not merely applying its ruling in *Glynn* to Plaintiffs, but has repeatedly urged Plaintiffs to come forward with evidence as to why their claims are not preempted, is giving Plaintiffs another opportunity in the context of the OTSC to present arguments to the Court as to why their claims are not preempted, and is applying the Rule 56 standard in doing so.

The Court has consistently made clear that it expected Plaintiffs to present all of the pertinent evidence on the issue of preemption by the end of the *Glynn* trial. Thus, Plaintiffs' argument that they have been denied the opportunity to develop expert testimony relevant to the preemption issue is ill-advised. The Court is also satisfied that additional individualized factual discovery is unnecessary because the crux of the preemption inquiry focuses on the relationship between Merck and the FDA, and has nothing to do with the facts or injuries of the individual Plaintiffs.[7] Stated differently, facts relating to *each individual Plaintiff* will not have any effect on whether *Merck* had a duty to warn, and testimony from individual experts regarding what Merck and the FDA *could* or *would* have done will not change what Merck and the FDA *did*.

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[7] Individualized discovery may be appropriate if the parties were disputing *causation* such as the Plaintiffs in *TMI*; however, the preemption analysis here is dependent on whether *Merck* had a state law *duty* to update its warning label.

Accordingly, the Court finds that utilizing an OTSC to apply the *Glynn* ruling to those Plaintiffs' whose injuries occurred prior to September 14, 2010, without allowing additional discovery is not improper.

B. Design Defect and Other Non–Failure to Warn Claim Arguments

The parties each submitted briefing with respect to whether the Court should utilize the OTSC to apply the *Glynn* preemption ruling to Plaintiffs' design defect and other non-failure to warn claims. In support of their position, Plaintiffs' argue that the Court's preemption ruling in *Glynn* only applied to a state law failure to warn claim and therefore did not address, and cannot be applied to, state law claims for design defect, negligence, fraud, breach of warranties, consumer protection/deceptive trade practices, and unjust enrichment. Specifically, Plaintiffs' argue that these claims do not "emanate from a general theory that Merck failed to provide an adequate warning about the risk of atypical femur fractures" and therefore, Defendant has not met its Rule 56 burden to obtain summary judgment on these claims. *See Plaintiffs' Design Defect Brief*, at p. 8.

i. Design Defect and Other Non–Failure to Warn Claim Analysis

As discussed in the procedural analysis, Merck's Rule 56 burden surrounding preemption was met by way of the briefing in *Glynn*. Plaintiffs' contention that applying the *Glynn* ruling to design defect and other non-failure to warn claims would improperly relieve Merck of its burden to show that it is entitled

to judgment on such claims is, in the abstract, persuasive. Importantly, however, Plaintiffs' design defect and other non-failure to warn claims are based entirely on the premise that Fosamax had risks which should have been disclosed to consumers. Thus, these claims rise and fall with a claim for failure to warn and utilizing an OTSC to preempt Plaintiffs' design defect and other non-failure to warn claims based on this Court's ruling in *Glynn* is not improper. *See Cooper v. Bristol–Myers Squibb Co.*, 2013 WL 85291, at *9 (D.N.J. Jan. 7, 2013) ("Therefore, having already determined that Plaintiff is unable to establish any triable issue with respect to his failure-to-warn claim, Plaintiff's design claim correspondingly fails."); *Begley v. Bristol–Myers Squibb Co.*, 2013 WL 144177, at * 9 (D.N.J. Jan. 11, 2013) ("... [A] product bearing an adequate warning is not in [a] defective condition, nor is it unreasonably dangerous ... Hence, Plaintiff's defective design claim fails because she has not demonstrated that the [product's] warning was inadequate." (internal citations omitted)); *Stafford v. Wyeth*, 411 F.Supp.2d 1318, 1320 (W.D.Okla.2006) (granting summary judgment to Defendant where plaintiff failed to establish that Defendant's failure to warn was the proximate cause of her injury and plaintiff's non-failure to warn claims, including negligence and design defect, "all hinge on defendant's alleged failure to warn."); *Chatman v. Pfizer, Inc.*, 2013 WL 1305506, at * 4 (S.D.Miss. Mar.28, 2013) ("... [T] he national consensus is that [plaintiff's] other claims are poorly camouflaged failureto-warn claims, and therefore most courts have rebuffed plaintiffs' attempts to recover under alternative state-law

theories of liability including negligence and fraud ... If [plaintiff's] remaining claims are disguised failure-to-warn claims, then they are unquestionably subject to [the failure to warn] preemption analysis" ... Further, "[t]here can be no doubt that [plaintiff's design defect] claims are [also] based on the inadequacy of the warning she was given, and therefore these claims are subject to [preemption] ..." (internal citation omitted)).

Plaintiffs' contend that neither their negligent design defect nor strict liability design defect claims sound in failure to warn, but that fact questions exist as to whether Fosamax was unreasonably dangerous, or whether Merck was negligent in failing to conduct adequate testing and use due care in the design and manufacture of Fosamax. In support of this argument, however, Plaintiffs' advance only a summary of the law and tests that may be applied to determine if a product is defectively designed but offer no law as to which test applies here and no facts and/or evidence to show that Fosamax was in fact defectively designed or that Merck acted negligently. Further, aside from the pleadings, this appears to be the first time in a six (6) year-long litigation, after a two (2) year focus on preemption, discovery, numerous briefs on the preemption issue and an entire trial worth of evidence, that Plaintiffs' believe Fosamax was defectively designed or that Merck was negligent in conducting testing of the drug. The entire MDL has centered on Merck's conduct in failing to update Fosamax's warning label.

To this end, Plaintiffs' make a conclusory statement that their complaints have "typically

alleged" facts in support of their non-failure to warn, strict liability and negligence based design defect claims, but offer no facts as to which, or how many Plaintiffs have in fact pled such claims. Plaintiffs' are conflating the standard to withstand a Federal Rule of Civil Procedure 12(b)(6) motion to dismiss with the standard to be applied here, which is that of a Rule 56 motion for summary judgment. Surely, Plaintiffs general description of what some complaints "typically allege" may constitute plain statements showing that Plaintiffs are entitled to relief, *see Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 557, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007); however, meeting the threshold requirement of Rule 12(b)(6) is hardly sufficient to defeat Merck's showing that it is entitled to judgment as a matter of law on preemption grounds.

Indeed, Merck has met this burden. Plaintiffs' design defect and other non-failure to warn claims are merely disguised failure to warn causes of action, which is evidenced by the pleadings that Plaintiffs attach as exhibits in response to the OTSC and the fact that the entire litigation, focus of the parties' discovery, and evidence put before the Court has been based entirely on Fosamax's warning. In fact, one of the complaints cited to by Plaintiffs in support of the argument that the design defect claims are independent of the warning specifically states that "Fosamax, as researched, tested, developed, designed, licensed, manufactured, packaged, labeled, distributed, sold and marketed by Defendant *was defective due to inadequate warnings and instructions.*" *See* [docket # 2996, *Ecklund Dec.*, Ex. 167 at ¶ 97 (emphasis supplied)]. Plaintiffs have not

alleged that Fosamax's chemical composition could have been changed, but rather, that the product was unreasonably dangerous because it was not accompanied by a proper warning. Similarly, Plaintiffs' negligent design defect claims allege that Merck failed to properly test the drug, and had Merck exercised due care in testing the product, Fosamax's label would have been updated sooner. Again, however, these contentions are nothing more than speculation and while Plaintiffs' design defect and other non-failure to warn arguments begin by focusing on the product and/or Merck's conduct on the front end, they conclude by focusing on how the consequence—the label—*may* have been different as a result. *See Estate of Popolizio v. Ford Motor Co.*, 2013 U.S. Dist. LEXIS 79361, at *5–6, 2013 WL 2459878 (D.N.J. June 5, 2013) ("the non-moving party cannot rely on unsupported assertions, bare allegations, or speculation to defeat summary judgment.").

The Court also disagrees with Plaintiffs' contention that state law design defect claims cannot be preempted under the federal Food, Drug, and Cosmetic Act ("FDCA"). Plaintiffs make this assertion by stating that every Federal Circuit Court to address whether the FDCA preempts design defect claims has found no preemption; however, instead of providing the Court with an analysis of how, or if, the cases are even applicable to the facts here, Plaintiffs merely list the case names and citations. As Merck correctly points out, the cases cited to by Plaintiffs are distinguishable from the instant matter and

therefore, carry little weight with respect to whether Plaintiffs' design defect claims can be preempted.[8]

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[8] In *Desiano v. Warner–Lambert & Co.*, 467 F.3d 85 (2d Cir.2006), the Second Circuit held that because Plaintiff's state law causes of action merely required *some* proof of fraud on the FDA but such proof was not conclusive, the Supreme Court's holding in *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) that all fraud on the FDA claims are preempted did not apply to *automatically* preempt Plaintiff's state law claims which only incidentally involved fraud. The Court in *Desiano* did note that state based tort liability falls within a state legislature's prerogative to regulate matters of health and safety and therefore, a presumption against preemption should apply; however, the Court went on to state that "there may be reasons to override that presumption [against preemption]." *See Desiano*, 467 F.3d at 94. Here, however, the Court is not applying preemption based on a fraud on the FDA theory to *automatically* preempt Plaintiffs' remaining claims that *incidentally* relate to fraud but rather, after giving Plaintiffs' an opportunity to be heard, is applying preemption based on a failure to warn ruling to preempt Plaintiffs' remaining claims that are based entirely on this same theory.

Abbot by Abbot v. Am. Cyanamid Co., 844 F.2d 1108 (4th Cir.1988) is similarly distinguishable to the instant matter because there, the Court was faced with a preemption analysis specific to vaccines. Notably, as the Abbot Court pointed out, Congress expressly dealt with vaccines in 1986 and 1987 and did not preempt state law; thus, the legislative intent surrounding vaccines weighed against preemption. Further, the Court's holding ultimately stands for the proposition that preemption is not *automatic*, as the Court stated that "[p]reemption does not follow *immediately* from the comprehensive federal regulation of prescription biological products. Every subject that merits congressional legislation is, by definition, a subject of national concern. That cannot mean, however, that every federal statute [automatically] ousts all related state law." *Id.* at 1112

Accordingly, because Plaintiffs' design defect and other non-failure to warn claims are entirely based, and ultimately hinge, on the adequacy of Fosamax's warning, these claims are preempted and must fail as a matter of law. Regardless of what state law applies to each Plaintiff's individual design defect and other non-failure to warn claims, Merck simply cannot be liable for not having a warning on its product that was rejected by the FDA as of the date of a Plaintiff's injury. Because the Court has already found that pursuant to *Wyeth v. Levine*, clear evidence exists

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(emphasis suppl ied) (i nternal citation omitted). The other cases cited to by Plaintiffs' reach a similar conclusion when dealing with vaccines. *See Hurley v. Lederle Labs. Div. of Am. Cyanamid Co.*, 863 F.2d 1173, 1178 (5th Cir.1988) ("... we believe that any case for preemption is doomed by the National Childhood Vaccine Injury ["NCVI"] Act of 1986."); Graham by *Graham v. Wyeth Labs., Div. of Am. Home Products Corp.*, 906 F.2d 1399, 1405 (10th Cir.1990) (indicating that federal preemption does not automatically apply to bar plaintiff's state tort law claims relating to an improperly manufactured vaccine just because such vaccine met the FDA's minimum standards. (emphasis supplied)).

Similarly *Wimbush v. Wyeth*, 619 F.3d 632 (6th Cir.2010) dealt with whether state law claims relating to negligence by a defendant that occurred prior to FDA approval are preempted by the FDA's subsequent approval of the drug. There, the Court specifically stated that it "hold[s] *merely* that FDA approval does not *automatically* preempt state law tort claims for negligence." *Id.* at 646 (emphasis supplied). Further, the Court notes that, of all the cases cited to by Plaintiffs' in support of their argument that design defect claims are not preempted by the FDCA, *Wimbush* is the only case that was decided after *Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009), and notably, *Wimbush* has the most narrow holding with respect to preemption.

that the FDA would have rejected a stronger warning label, and the crux of Plaintiffs' design defect and non-failure to warn claims is the adequacy of the warning, Defendant is entitled to summary judgment on these claims.

C. Adverse Reaction and Long–Term–Use Failure to Warn Arguments

Plaintiffs argue that their failure to warn claims cannot be preempted because *Glynn* was specific to Merck's failure to update the Precautions section of the Fosamax label, but that Merck has not met its burden to show clear evidence exists that the FDA would have rejected a change to the Adverse Reactions section of the label or a change relating to the long-term use/shifting risk-benefit profile of Fosamax. While Plaintiffs acknowledge that Merck did in fact update the Adverse Reactions section of the Fosamax label in June 2009, Plaintiffs argue that a genuine dispute of fact exists as to whether Merck could have updated the Adverse Reactions section of the label *before* that time.

i. Adverse Reaction and Long–Term Use Analysis

There are several issues surrounding Plaintiffs' arguments. First, as stated above, Merck updated the Adverse Reactions section of its label in June, 2009. The OTSC has instructed Plaintiffs' with injuries occurring prior to September 14, 2010, to show cause why their claims should not be preempted. Upon review of the Plaintiffs' listed in Appendix A of the OTSC, nearly half of them have injuries which occurred between June, 2009 and September 14, 2010. Thus, to state that Plaintiffs'

failure to warn claims are not preempted because they are based on the Adverse Reactions section of the label and not the Precautions section is illogical. Rather, almost half of the Plaintiffs identified in the OTSC were injured when there was *already* an Adverse Reactions warning on the label[9]; therefore, the only plausible failure to warn claims available to such Plaintiffs would have to be based on the Precautions section.

Second, to the extent that Plaintiffs' injuries occurred prior to the June, 2009 Adverse Reactions label change, Plaintiffs assert that there is evidence showing that a fact question exists with regard to whether Merck should have updated this section of the label sooner. As an initial matter, Plaintiffs do not plead this theory of liability in any of their complaints, nor have Plaintiffs set forth evidence indicating that any doctor would not have prescribed Fosamax if the occurrence of low-energy femoral shaft fractures had been mentioned in the Adverse Reactions section prior to 2009. Further, Plaintiffs' argument is one that was already made—also at the last hour—in *Glynn* and, prior to trial, Plaintiffs asserted that the evidence would show that Merck should have acted sooner to report the information it was receiving about fractures to the FDA. *Hearing Tr.*, 71:20–22; 72:8–10, March 8, 2013 ("M R. HONNOLD: The argument is, is the data was clearly there and **the evidence will be** Merck did not act upon it ... it could have and should have been done

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[9] Plaintiffs do not dispute the adequacy of the Adverse Reactions label.

differently based upon the information that Merck had in its possession and sat on and did nothing with.") (emphasis supplied); see also *Plaintiff's Preemption Supplement in Opposition to Defendant's Motion for Summary Judgment Based Upon Federal Preemption, Rule 50(a), and Rule 50(b) Motions* [docket # 218 at 11–5304] ("[T]here is considerable evidence demonstrating that Merck should have at a minimum updated the [A]dverse [R]eactions section of its label as early as 1999.").

This argument is again dependent on the communication of information between *Merck* and the *FDA*, and is of no consequence to the individual Plaintiff. Plaintiffs presented evidence on this issue during the *Glynn* trial and argued that such evidence proves that Merck should have acted sooner; however, this Court was not convinced. The argument being presented by Plaintiffs now is no different than that which was already considered in *Glynn* because the evidence relevant to this claim is what *Merck* submitted to the *FDA* and such communications are the exact same regardless of which Plaintiff is before the Court. Thus, as in *Glynn*, the Court is still not convinced and Plaintiffs cannot recharacterize their failure to warn claims at this stage of the litigation as one involving the Adverse Reactions section of the label in order to overcome the preemption issue. *See In re Fosamax Prods. Liab. Litig. (Boles v. Merck & Co.)*, 2010 WL 1257299, at *5 (S.D.N.Y. Mar.26, 2010) ("[Plaintiff] cannot recharacterize her claim during trial in an effort to overcome the lack of evidence ...").

Third, Plaintiffs' risk-benefit argument surrounding the efficacy of Fosamax was also already considered in *Glynn*. The Court did not accept Plaintiffs' efficacy argument in *Glynn* for the same reason it will not accept this argument here: the omission of efficacy information does not constitute a failure to warn about a drug's risks and therefore, does not raise a genuine issue of material fact as to whether Plaintiffs' failure to warn claims are preempted. *See LaBarre v. Bristol–Myers Squibb Co.*, 2013 WL 6053840, at * 4 (3d Cir. Nov.18, 2013) ("In short, [the drug's] efficacy is irrelevant to [Plaintiff's] failure to warn claim, and the physicians' purported lack of information about it is of no consequence to the adequacy of the warnings.").

In sum, Plaintiffs' contention that the Adverse Reaction section of the label should have been updated prior to 2009, or that efficacy information should have been communicated on the Fosamax label, do not fall outside the scope of *Glynn* and the OTSC nor do they raise genuine issues of material fact with regard to whether clear evidence exists that the FDA would have rejected a label change. Accordingly, Plaintiffs' failure to warn claim(s) are preempted.

D. Warnings and Precautions Failure to Warn Arguments

Plaintiffs argue that their failure to warn claims are not preempted because communications from the FDA reflect that clear evidence does not exist as to whether the FDA would have rejected a warning that was accurately stated and properly supported by Merck. In support of this argument, Plaintiffs

contend that Merck misstated the relevant risk in its PAS submission and the FDA's rejection of Defendant's proposed label is not clear evidence because the agency lacked information to make an informed judgment.

i. Warnings and Precautions Failure to Warn Analysis

Plaintiffs' argument that its claims are not preempted because clear evidence does not exist as to whether the FDA would have rejected a stronger warning to the Precautions section of the label is nothing more than an attempt to gain a second bite at the apple. Plaintiffs fail to raise any facts and/or arguments with regard to the Precautions section of the label that were not already considered and rejected by this Court. Plaintiffs assert that there is new evidence which was not before the Court in *Glynn* that changes the Precautions analysis; however, the "new evidence" provided by Plaintiffs is merely expert opinion on the very same evidence that existed in *Glynn*. Stated differently, while Plaintiffs were able to find an expert to agree with their contention that Merck should have acted differently with respect to updating the Precautions section of its warning, they did not set forth any evidence which suggests that *the FDA* thought the same. The evidence surrounding whether the FDA felt that a label change was necessary remains unchanged, and importantly, provides clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning. *See Glynn*, 2013 WL 3270387, at *7 ("the [fact that the] FDA never required Defendant to

submit new language or change the label [ ] demonstrate [s] that the FDA did not think that the label should have been changed at that time.").

Plaintiffs further rely on this new expert opinion to argue that a fact question exists as to whether Merck should have warned about the risk of fractures associated with Fosamax by way of a CBE submission while the FDA decided on class labeling. Again, however, the Court already rejected this argument in *Glynn* and stated that "since the FDA rejected Defendant's PAS, it would not have approved a CBE seeking to add the same language to the label that it just rejected in the PAS, and any changes Defendant made using the CBE supplement would cause the drug to be misbranded." *Id.* at * 8.

Moreover, to the extent that Plaintiffs claim that Merck withheld information from the FDA and clear evidence does not exist as to whether the FDA, if fully informed, would have rejected a stronger label, this does not defeat Defendant's showing that it is entitled to judgment as a matter of law on preemption grounds. As an initial matter, Defendant disputes that it withheld information from the FDA; however, even assuming it did, Plaintiffs have failed to show that providing such information to the FDA would have changed the FDA's conclusion that a Precaution was not warranted. Instead, Plaintiffs' contention appears to be a fraud-on-the FDA theory which was rejected by the Supreme Court in *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001), or alternatively, is based largely on speculation and cannot defeat summary judgment. *See Webster v.*

Pacesetter, Inc., 259 F .Supp.2d 27, 37 (D.D.C.2003) ("Nor can plaintiffs create an issue of fact regarding their defective warning claim by speculating that *if* the FDA had known of the delayed perforation and tamponade incidents during the clinical trials and *if* defendant had investigated all the adverse incidents, the FDA would have either recalled the lead or placed it on alert." (emphasis in original)); *In re Trasylol Products Liab. Litig.*, 2010 WL 4259332 (S.D.Fla. Oct.21, 2010) ("[An expert] may not speculate as to what the FDA would have done in hypothetical circumstances.").

Accordingly, Plaintiffs have failed to show that there is a genuine dispute of fact surrounding failure to warn claims based on the Precautions section of the label. Thus, these claims are preempted and Defendant is entitled to judgment as a matter of law.

IV. CONCLUSION

For the reasons outlined above, Defendant is entitled to judgment as a matter of law on all claims made by the Plaintiffs listed in Appendix A of the OTSC with injuries that occurred prior to September 14, 2010, because Plaintiffs have failed to show cause why their claims are not preempted under this Court's ruling in *Glynn*. An appropriate Order accompanies this Opinion.

All Citations

Not Reported in F.Supp.2d, 2014 WL 1266994

APPENDIX D

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.

Bernadette Glynn and Richard Glynn, Plaintiffs,

v.

Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.

United States District Court,
D. New Jersey.
June 27, 2013.

Donald A. Ecklund, James E. Cecchi, Carella Byrne Cecchi Olstein Brody & Agnello, P.C., Roseland, NJ, Christopher A. Seeger, David R. Buchanan, Seeger Weiss LLP, Newark, NJ, Edward Braniff, Weitz & Luxenberg, New York, NY, for Plaintiffs.

David J. Heubeck, Venable LLP, Baltimore, MD, Karen A. Confoy, Fox Rothschild LLP, PC, Lawrenceville, NJ, for Defendant.

OPINION

PISANO, District Judge.

Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") brought this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), the manufacturer of Fosamax, which is a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation ("MDL") concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs'[1]"), it caused Plaintiff Mrs. Glynn's femur fracture, and Defendant failed to warn physicians about Fosamax and AFFs. Presently before the Court is Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25], Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 198], Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(a) [docket # 209], and Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216]. The issue in these Motions and before the Court is whether there is clear evidence that the FDA would not have approved a stronger warning to the Fosamax label, thereby warranting preemption of Plaintiffs' failure to warn claim. *See Wyeth v. Levine*, 555 U.S. 555, 129 S.Ct. 1187, 173 L.Ed.2d 51 (2009). This Court heard oral argument on the federal preemption issue on March 8, 2013 and reserved decision until a trial record had been established.

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[1] The abbreviation of atypical femur fracture (singular) is "AFF."

See Fed.R.Civ.P. 78. A jury trial took place from April 8, 2013 to April 29, 2013. On April 29, 2013, the jury returned a verdict for Defendant, finding that Plaintiff did not prove by a preponderance of the evidence that she experienced an AFF in April 2009. Because the record contains clear evidence that the FDA would not have approved a stronger warning to the Precautions section of the Fosamax label, this Court grants the Motions on federal preemption.

I. BACKGROUND[2]

A. Fosamax Approval & Mrs. Glynn's Fosamax Use

In September 1995, the FDA approved Fosamax for the treatment of osteoporosis in postmenopausal women, and in April 1997, the FDA approved Fosamax for the prevention of osteoporosis in postmenopausal women. Since this time, Fosamax has remained FDA approved for the treatment and prevention of postmenopausal osteoporosis.

In 2002, Dr. Murat Acemoglu first prescribed Fosamax to Mrs. Glynn after diagnosing her with "osteopenia—osteoporosis" [docket # 27, Confoy Dec., Ex. 27 & 28]. Mrs. Glynn took Fosamax until April 17, 2009, when she fractured her right femur. Final Pretrial Order ¶ 3.

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[2] This Background section contains facts that pertain to the federal preemption issue. For a more complete discussion of the facts of this case, see this Court's Opinion dated April 11, 2013, 2013 WL 1558697 [docket # 183].

B. History of Fosamax Label Change

On June 13, 2008, the FDA contacted Defendant and other bisphosphonate [3] manufacturers and requested any investigations they conducted "regarding the occurrence of atypical fractures with bisphosphonate use," any investigational plans, and "all hip and femoral fracture case reports" they received [docket # 26, Declaration of Karen A. Confoy in Support of the Motion for Summary Judgment and Motion for Summary Judgment Based Upon Federal Preemption ("Confoy Dec."), Ex. 5; docket # 27, Confoy Dec., Ex. 4]. The FDA also asked that Defendant and the other bisphosphonate manufacturers make an effort where possible "to clarify the fracture location and the duration of bisphosphonate exposure for all case reports." *Id.* The FDA explained that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates" and is "concerned about this developing safety signal." *Id.*

On July 18, 2008, Defendant responded to the FDA's request and included summary tables of clinical and post-marketing data, clinical Council for International Organizations of Medical Sciences ("CIOMS") reports, and post-marketing CIOMS reports [docket # 27, Confoy Dec., Ex. 6]. The FDA's review of this data as well as the data from other bisphosphonate manufacturers "did not show an increase in . . . [the risk of atypical subtrochanteric femur fractures] in women using these medications" [docket # 26, Confoy Dec., Ex. 7].

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[3] Fosamax belongs to a class of drugs known as bisphosphonates.

On September 15, 2008, Defendant submitted a Prior Approval Supplement ("PAS") to the FDA, proposing "to add language to both the Precaution[s] and Adverse Reactions/Post–Marketing Experience section[s] of the label to describe low-energy" subtrochanteric femoral fractures [docket # 27, Confoy Dec., Ex. 8]. Defendant explained that "[i]t is not possible with the present data to establish whether treatment with" Fosamax "increases the risk of [these] . . . low-energy subtrochanteric and/or proximal shaft fractures," but because there is a temporal association between these fractures and Fosamax, Defendant thought that it was "important to include an appropriate statement about them in the product label." *Id.* Defendant sought to add the following language to the Precautions section of the label:

> Low–Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonatetreated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use,

> previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.
>
> [*Id.*]

Additionally, Defendant proposed adding "low-energy femoral shaft fracture" to the Adverse Reactions/Post–Marketing Experience section of the label and the following statement to the Patient Package Insert: "Patients have experienced fracture in a specific part of the thigh bone. Call your doctor if you develop new or unusual pain in the hip or thigh." *Id.*

On April 15, 2009, an FDA representative e-mailed Defendant and stated that the proposed label change to the Adverse Reactions/Post–Marketing Experience section of the label would be approved but the label change to the Precautions section would not be approved [docket # 101, Cecchi Dec., Ex. 83; docket # 27, Confoy Dec., Ex. 10]. Two days later, Mrs. Glynn fractured her femur.

On May 22, 2009, one month after Mrs. Glynn's fracture, the FDA formally responded to Defendant's proposed label change, recommending that it add "low energy femoral shaft and subtrochanteric fractures" to the Adverse Reactions/Post–Marketing Experience section of the label; however, the FDA did not approve the label change to the Precautions section [docket # 27, Confoy Dec., Ex. 11]. Moreover,

the FDA warned that Fosamax "may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if [it is] ... marketed with" these label changes "before [FDA] approval. . . ." *Id.*

On July 2, 2009, Defendant submitted to the FDA a Changes Being Effected ("CBE") supplement to add information about femur fractures to the Adverse Reactions/Post–Marketing Experience section of the label because the FDA told Defendant that submitting a CBE supplement was the "quickest route to update the [Product Circular] PC" for Fosamax [docket # 27, Confoy Dec., Ex. 12]. On March 1, 2010, the FDA approved the CBE supplement [docket # 26, Confoy Dec., Ex. 9].

On March 10, 2010, the FDA issued a Drug Safety Communication, in which it stated that "[a]t this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" [docket # 26, Confoy Dec., Ex. 5]. The FDA did state, however, that it was "working closely with outside experts, including members of the ... American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue." *Id.*

On September 14, 2010, the American Society for Bone and Mineral Research ("ASBMR") published an article entitled *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral*

Research [docket # 26, Confoy Dec., Ex. 13].[4] The report stated that although there is an association between long-term bisphosphonate use and AFFs, the association has "not been proven to be causal." *Id.* at 2269, 2287. The report concluded that although AFFs are rare, "they appear to be more common in patients who have been exposed to long-term BPs [("bisphosphonates")], usually for more than 3 years. . . ." *Id.* at 2287. The report further provided that although "BPs are important drugs for the prevention of common osteoporotic fractures," "atypical femoral fractures are of concern, and more information is urgently needed both to assist in identifying patients at particular risk and to guide decision making about duration of BP therapy.

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[4] In this report, the ASBMR defined AFF by listing its Major Features, which are required to satisfy the definition of AFF, and Minor Features, which may be associated with AFFs but are not required characteristics of them [docket # 26, Confoy Dec., Ex. 13]. The Major Features of an AFF are: (1) that it is "located anywhere along the femur from the distal to the lesser trochanter to just proximal to the supracondylar flare"; (2) "associated with no trauma or minimal trauma, as in a fall from a standing height or less"; (3) transverse or short oblique configuration; (4) noncomminuted; and (5) complete fractures extend through both cortices and may be associated with a medial spike, incomplete fractures involve only the lateral cortex. *Id.* The Minor Features of an AFF are: (1) localized periosteal reaction of the lateral cortex; (2) generalized increase in cortical thickness of the diaphysis; (3) prodromal symptoms such as dull or aching pain in the groin or thigh; (4) bilateral fractures and symptoms; (5) delayed healing; (6) comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hyposphosphotasia); and (7) use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, and proton pump inhibitors). *Id.*

Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs." *Id.*

The FDA responded to the report by issuing a Drug Safety Communication, in which it stated "[a]lthough it is not clear if bisphosphonates are the cause [of AFFs], these unusual femur fractures have been identified in patients taking these drugs" [docket # 26, Confoy Dec., Ex. 14]. Additionally, the FDA informed that the "optimal duration of bisphosphonate treatment for osteoporosis is unknown" but "clinical trial data . . . support[s] effectiveness for the reduction of common bone fractures for three to five years." *Id.* Regarding the ASBMR Task Force's recommendation of a label change, the FDA stated that it "has assembled and is thoroughly reviewing all long term data available on the products, as well as all safety reports, and *is considering* label revisions." *Id.* (emphasis added).

In October 2010, the FDA issued another Drug Safety Communication, informing that it would require all bisphosphonate manufacturers to add information on AFFs to the Precautions section of the drug labels and require a new Limitations of Use statement in the Indications and Usage section of the label because "these atypical fractures may be related to long-term . . . bisphosphonate use" [docket # 26, Confoy Dec., Ex. 15]. It reiterated that "[a]lthough it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates." *Id.* On January 11, 2011, Defendant submitted the agreed upon label changes to the FDA [docket # 27,

Confoy Dec., Ex. 18]. Also in January 2011, the FDA issued an update on femur fractures and bisphosphonate use, stating "[a]lthough it is not clear that the drugs are a direct cause of these unusual fractures, they have mainly been reported in patients taking bisphosphonates" [docket # 26, Confoy Dec., Ex. 19].

Currently, the Fosamax label includes the following language: "Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. . . . Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area" [docket # 26, Confoy Dec., Ex. 20].

C. Procedural History

On September 15, 2011, Plaintiffs filed a Complaint in this Court against Defendant, alleging causes of action for: (1) failure to warn; (2) defective design; (3) negligence; (4) negligent misrepresentation; (5) breach of express warranty; (6) breach of implied warranty of fitness for a particular purpose; (7) breach of implied warranty of merchantability; (8) violation of the Consumer Fraud Act, N.J.S.A. 56:8–2 et seq.; (9) violations of the New York General Business Law, N.Y. Gen. Bus. Law §§ 349 et seq. and 350 et seq.; (10) unjust enrichment; (11) punitive damages pursuant to the New Jersey Product Liability Act, N.J.S.A. 2A:58C–1 et seq., and the New Jersey Punitive Damages Act, N.J.S.A. 2A:15–5.10, et seq.; and (12) loss of

consortium on behalf of Plaintiff Richard Glynn [docket # 1]. [5] Defendant moved for summary judgment based on federal preemption on January 15, 2013, arguing that Plaintiffs' claims, all of which ultimately concern a failure to warn, are preempted because the FDA rejected Defendant's proposed label change and this constitutes clear evidence that the FDA would not have approved a stronger warning to the Precautions section of the label [docket # 25]. On March 8, 2013, the Court heard argument on the preemption issue and reserved decision on it [docket # 138]. On April 2, 2013, the Court reserved decision on the federal preemption motion until there was a complete trial record in the case [docket # 156].

Trial began on April 8, 2013 and concluded on April 29, 2013. After the close of the Plaintiff's case, on April 20, 2013, Defendant filed a Motion for Judgment as a Matter of Law pursuant to Federal Rule of Civil Procedure 50(a) [docket # 198]. Defendant argued that although it submitted to the FDA all the information relevant to a label change and tried to change the Precautions section of the label to include low-energy femoral fractures, the

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[5] Subsequently, Plaintiffs decided to pursue only the following claims: (1) failure to warn; (2) breach of the implied warranty of fitness for a particular purpose; (3) violations of the New York General Business Law; and (4) punitive damages. The Court granted summary judgment on the New York General Business Law claims [docket # 183]. In addition, the Court granted a Motion for Judgment as a Matter of Law as to the breach of implied warranty of fitness for a particular purpose claim and punitive damages [docket # 198]. Trial Tr. 1896:2–17; 2586:20–22. Thus, the failure to warn claim is the only claim that remains. Trial Tr. 2586:11–12.

FDA rejected the label change. On April 26, 2013, Defendant renewed its Motion for Judgment as a Matter of Law, again arguing that Plaintiffs' claims are preempted because Defendant proposed a change to the Precautions section of the Fosamax label and the FDA rejected it [docket # 209]. On April 29, 2013, the jury returned a verdict for Defendant, finding that Plaintiffs did not prove by a preponderance of the evidence that Mrs. Glynn experienced an AFF in April 2009. The following day, the Court held an in-person status conference to discuss the preemption issue as well as other MDL issues. The Court explained that it previously deferred decision on the preemption issue for "a complete record" and "the best way to do that was to try the" case. Hearing Tr., 6:10–14, April 30, 2013. Although Plaintiffs had several opportunities to present evidence on preemption, they requested additional time to present more evidence on the issue. The Court gave Plaintiffs twenty-one days to submit "proposed fact findings that are based upon the record in opposition to" the preemption motions. *Id.* at 19:24–20:1. Thereafter, on May 6, 2013, Defendant submitted a Renewed Motion for Judgment as a Matter of Law pursuant to Rule 50(b) [docket # 216]. Plaintiffs submitted an opposition brief and Defendant submitted a reply brief.

II. DISCUSSION

A. Standard

"If a court does not grant a motion for judgment as a matter of law made under Rule 50(a), the court is considered to have submitted the action to the jury

subject to the court's later deciding the legal questions raised by the motion." Fed.R.Civ.P. 50(b). The movant may then file a renewed motion for judgment as a matter of law, and in "ruling on the renewed motion, the court may: (1) allow judgment on the verdict, if the jury returned a verdict; (2) order a new trial; or (3) direct the entry of judgment as a matter of law." *Id.*

B. Plaintiffs' Claims Are Preempted

Defendant argues that Plaintiffs' claims are preempted under federal law because it proposed a label change to the Precautions section of the Fosamax label to include a warning about low-energy femur fractures, and the FDA rejected the label change after Mrs. Glynn's fracture. Defendant asserts that this constitutes clear evidence that the FDA would have rejected any warning about these fractures prior to Mrs. Glynn's femur fracture. Moreover, Defendant contends that Plaintiffs' claims are preempted for three additional reasons: (1) Plaintiffs did not present evidence that the FDA rejected the proposed label change for using the phrase "stress fracture" as opposed to AFF; (2) Plaintiffs did not show that the label change could have been successfully presented through a CBE supplement; and (3) Plaintiffs did not show that Defendant withheld any information from the FDA.

Plaintiffs, however, argue that Defendant has not shown clear evidence that the FDA would have rejected language about AFFs in the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture. Plaintiffs assert that preemption is improper for the following reasons: (1) the FDA

rejected the PAS because Defendant used the phrase "stress fracture" instead of "atypical" fracture, and the FDA would have approved an appropriately worded warning; (2) Defendant could have changed the label through a CBE supplement; (3) Defendant did not provide all of the information it had on femur fractures and Fosamax to the FDA, and had it done so, the FDA would have approved a properly worded warning in 2008; and (4) Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association between Fosamax and AFFs.

Defendant submitted a reply brief, again arguing that preemption is proper because Defendant proposed a label change in 2008 and the FDA rejected it in 2009, after Mrs. Glynn's fracture. Defendant asserts that the FDA did not reject the label change because Defendant used the phrase "stress fracture" since references to "stress fractures" were included to aid in the early identification of low-energy femur fractures. Moreover, Defendant contends that it did not fail to submit information to the FDA. Lastly, Defendant points out that the evidence Plaintiffs presented in their brief was not introduced at trial and thus, is not properly before this Court on this Motion; even if it was properly before this Court, the evidence does not change the fact that clear evidence exists that the FDA would not have approved a stronger warning to the Fosamax label.

[1-6] The Supremacy Clause provides that the "Constitution, and Laws of the United States . . . shall be the supreme Law of the Land. . . ." U.S. Const. art. VI, cl. 2. It "invalidates state laws that interfere with, or are contrary to, federal law." *Hillsborough County, Florida v. Automated Medical*

Laboratories, Inc., 471 U.S. 707, 712, 105 S.Ct. 2371, 85 L.Ed.2d 714 (1985) (internal quotation omitted). Federal law preempts state law in three ways: (1) express preemption; (2) field preemption, and (3) conflict preemption. *Farina v. Nokia Inc.*, 625 F.3d 97, 115 (3d Cir. 2010), *cert. denied*, —— U.S. ——, 132 S.Ct. 365, 181 L.Ed.2d 231 (2011); *Dobbs v. Wyeth Pharmaceuticals*, 797 F.Supp.2d 1264, 1268 n. 3 (W.D.Okla.2011). Express preemption occurs when Congress states "in express terms" that it is preempting state law. *Hillsborough County, Florida*, 471 U.S. at 713, 105 S.Ct. 2371. Field preemption occurs when Congress intends to preempt state law "in a particular area" or in other words "the scheme of federal regulation is sufficiently comprehensive . . . [so] Congress 'left no room' for supplementary state regulation." *Id.* Conflict preemption is when a "state law is in actual conflict with federal law"; this exists "where it is impossible for a private party to comply with both state and federal requirements . . . or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine, a Div. of Brunswick Corp.*, 537 U.S. 51, 64, 123 S.Ct. 518, 154 L.Ed.2d 466 (2002) (internal quotation omitted). This case concerns conflict preemption because Defendant argues that it was impossible to comply with the state law duty to warn and the FDA's regulations[6] since Plaintiffs argue that

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[6] Federal regulations "preempt state laws in the same fashion as congressional statutes." *Farina*, 625 F.3d at 115 (citing *Fid. Fed. Sav. & Loan Ass'n. v. de la Cuesta*, 458 U.S. 141, 153, 102 S.Ct. 3014, 73 L.Ed.2d 664 (1982)).

a warning about low-energy femur fractures should have been included in the Fosamax label but the FDA rejected a proposed warning.

[7,8] Conflict preemption, however, "is a demanding defense." *Wyeth*, 555 U.S. at 573, 129 S.Ct. 1187. As a result, generally, FDA approval or compliance with FDA labeling regulations is not a complete defense to a state failure to warn claim. *Id.* at 559, 129 S.Ct. 1187. If, however, there is "clear evidence that the FDA would not have approved a change" to the prescription drug's label, then it is impossible to comply with both federal and state requirements[7] and the state failure to warn claim is preempted. *Id.* at 571, 129 S.Ct. 1187. *Wyeth* does not define "clear evidence," so "application of the clear evidence standard is necessarily fact specific." *Dobbs*, 797 F.Supp.2d at 1270.

[9] Here, preemption is warranted because there is clear evidence that the FDA would not have approved a change to the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture. In September 2008, Defendant submitted a PAS to the FDA, seeking to add language about low-energy femur fractures to the Precautions and Adverse Reactions sections of the label. In May 2009, approximately one month after Mrs. Glynn's fracture, the FDA sent Defendant a letter approving the change to the Adverse Reactions section of the label but denying

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[7] Federal regulations require that a drug's label "be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57.

the change to the Precautions section of the label. The FDA's rejection constitutes clear evidence that the FDA would not have approved a label change to the Precautions section of the label prior to Mrs. Glynn's injury. *See Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir.2010) (finding clear evidence that the FDA would not have approved a label change because the FDA did not approve "a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do so in a submission"); *Dobbs*, 797 F.Supp.2d at 1276–77 (finding clear evidence that the FDA would have rejected an expanded warning for Effexor after the FDA rejected the warning added by Defendant); *see also Wyeth*, 555 U.S. at 571–72, 129 S.Ct. 1187 (holding that *Wyeth* "failed to demonstrate that it was impossible for [it] ... to comply with both federal and state requirements" and reasoning that it "offered no such evidence" and never argued "that it attempted to give" a warning but "was prohibited from doing so by the FDA").

Indeed, the evidence presented at trial establishes that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to Mrs. Glynn's injury. In fact, Dr. Cheryl Blume ("Dr. Blume"), one of Plaintiffs' experts who was "central" to Plaintiffs' preemption analysis, testified that the FDA "rejected" Defendant's PAS. Hearing Tr., 12:24–13:13, April 2, 2013; Trial Tr., 661:10–14. Moreover, Dr. Lisa Rarick ("Dr. Rarick"), one of Defendant's experts who worked for the FDA for fifteen years, testified that the FDA "rejected a precaution" to the Fosamax label in their May 22, 2009 letter to Defendant. Trial Tr., 2436:22–24;

2501:7–9. Dr. Rarick further testified that although the FDA had the authority to ask Defendant to submit "alternative precautionary language" if it was "still contemplating [that] they might accept a precaution," the FDA did not do so, thereby indicating that it would not accept a label change to the Precautions section of the Fosamax label at that time. *Id.* at 2501:10–2502:1. Furthermore, Dr. Rarick testified that the FDA had the authority to request that Defendant "make a label change to include reports of low-energy spontaneous subtrochanteric or atypical femur fractures," but they never made such a request. *Id.* at 2485:4–8; 2578:2–12. Thus, clear evidence exists that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture because Defendant submitted a label change and the FDA rejected it, and the FDA never required Defendant to submit new language or change the label, which demonstrates that the FDA did not think that the label should have been changed at that time.

Plaintiffs did not present any evidence at trial to refute preemption. First, Plaintiffs did not offer any evidence that Defendant's PAS was rejected due to language, specifically the use of "stress fracture" instead of "AFF," or that the FDA would have approved a properly worded label change. Instead, it would have been improper for Defendant to use the term "AFF" in 2008 when they submitted the PAS because, as Dr. Blume testified, the phrase "atypical femur fractures . . . wasn't even contrived until 2010 or 2011." *Id.* at 725:22–24. In addition, Dr. Cornell, the Clinical Director of Orthopaedic Surgery at the Hospital for Special Surgery and one of Plaintiffs'

experts, explained that Fosamax "can lead to . . . subsequent stress fracture formation," and when he wrote about these fractures, he was "talking about atypical femur fractures." *Id.* at 1264:20–1265:8. Moreover, Dr. Rarick testified that in rejecting Defendant's PAS, the FDA did not conclude that the label was "confusing to doctors" or that "stress fractures didn't look as severe and significant as . . . atypical femur fractures"; instead, Dr. Rarick stated that the FDA rejected the PAS because the "data didn't support the precaution language." *Id.* at 2512:10–18. This testimony demonstrates that the FDA did not reject the PAS due to Defendant's use of the phrase "stress fracture." Not only was the phrase AFF not coined in 2008, but some doctors used "stress fracture" as a term to refer to low-energy subtrochanteric fractures.

Second, Plaintiffs did not offer any evidence that Defendant could have submitted a CBE supplement to change the Precautions section of the Fosamax label. A CBE supplement gives a "manufacturer . . . the ability to change the label without FDA approval." *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir.2010); *Dobbs*, 797 F.Supp.2d at 1271 (citing 21 C.F.R. § 314.70(c)(6)(iii)) (stating it is "an exception to the requirement of advance approval for label changes under certain circumstances"). A CBE supplement "allows a pre-approval label change by the manufacturer where the change is needed to add or strengthen a contraindication, warning, precaution or information about an adverse reaction." *Dobbs*, 797 F.Supp.2d at 1271 (citing 21 C.F.R. § 314.70(c)(6)(iii)(A)). Like a PAS, the "proposed change must be based on 'reasonable evidence of' an

association between a hazard and the drug at issue; however, a causal relationship need not have been definitely established." *Id.* (citing C.F.R. § 201.57(c)(6)(i)). After the label change has been affected, the "FDA has the opportunity to consider whether or not it will accept the change." *Mason*, 596 F.3d at 392. Drs. Blume and Rarick testified that if the FDA rejects a CBE label change, the manufacturer must change the label, otherwise it will be misbranded. Trial Tr. 733:16–734:9; 2502:8–16. Thus, since the FDA rejected Defendant's PAS, it would not have approved a CBE seeking to add the same language to the label that it just rejected in the PAS, and any changes Defendant made using the CBE supplement would cause the drug to be misbranded. In addition, Dr. Rarick testified that the FDA could have requested that Defendant submit the label change using the CBE instead of the PAS method, but the FDA did not do so. *Id.* at 2489:19–22. Moreover, Dr. Rarick opined that the CBE method was not "the appropriate method to submit" a label change regarding low-energy subtrochanteric femur fractures because this "topic . . . was under FDA's review. . . ." *Id.* at 2493:11–22. As a result, the evidence does not show that Defendant could have changed the Precautions section of the Fosamax label using a CBE supplement.

Third, Plaintiffs did not show that Defendant failed to provide all the information it had on femur fractures to the FDA and that Defendant failed to warn the FDA as soon as there was reasonable evidence of a causal association between Fosamax and AFFs. Instead, Dr. Blume and Dr. Santora, Defendant's employee who is responsible for Fosamax,

testified that Defendant supplied the Odvina report, Goh report, Adverse Event Reports, and data it obtained from physicians; Defendant also submitted information when the FDA requested it in 2008. *Id.* at 729:5–730:21; 2175:16–21; 2176:4–10; 2254:15–19; 2261:13–2262:8. Regarding the timing of Defendant's proposed label change, there is no evidence that Defendant failed to submit the label change when it had reasonable evidence of a causal association between Fosamax and femur fractures. Defendant submitted the PAS three months after the FDA requested information from bisphosphonate manufacturers, and as late as March 2010, the FDA did not see a "clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures" [docket # 26, Confoy Dec., Ex. 5].

[10] Not only did Plaintiffs fail to offer any evidence at trial to refute preemption but the exhibits Plaintiffs cited in their opposition brief were not presented at trial [docket # 218]. This is inappropriate on a Motion for Judgment as a Matter of Law where "the court is limited to the trial record and nothing else." *Laymon v. Lobby House, Inc.*, 613 F.Supp.2d 504, 510 (D.Del.2009). Even if the evidence Plaintiffs cited were part of the trial record, this Court is not persuaded that it would change the fact that there is clear evidence that the FDA would not have approved a stronger warning prior to Mrs. Glynn's fracture.

Therefore, preemption is warranted in this case. Defendant submitted a PAS in 2008 seeking to change the Precautions section of the Fosamax label to include information on low-energy subtrochanteric

femur fractures, but the FDA rejected the PAS in May 2009, one month after Mrs. Glynn's fracture. This constitutes clear evidence that the FDA would not have approved a stronger warning prior to Mrs. Glynn's fracture. Although Plaintiffs have had several opportunities to introduce evidence in opposition to preemption, they have not refuted the fact that clear evidence exists. Consequently, based on the record before the Court, Plaintiffs' failure to warn claim is preempted.

III. CONCLUSION

For the reasons outlined above, this Court grants Defendant's Motion for Summary Judgment based upon Federal Preemption [docket # 25], Motion for Judgment as a Matter of Law [docket # 198], second Motion for Judgment as a Matter of Law [docket # 209], and Renewed Motion for Judgment as a Matter of Law [docket # 216] and enters judgment in favor of Defendant. An appropriate Order accompanies this Opinion.

APPENDIX E

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 14-1900

IN RE: FOSAMAX (ALENDRONATE SODIUM)
PRODUCTS LIABILITY LITIGATION

D. N.J. 3:08-cv-00008-FLW *et al.*, MDL No. 2243

SUR PETITION FOR REHEARING

Present: SMITH, Chief Judge, AMBRO, CHAGARES, JORDAN, HARDIMAN, VANASKIE, SHWARTZ, KRAUSE, RESTREPO, FUENTES,* Circuit Judges

The petition for rehearing filed by appellant, in the above-entitled case having been submitted to the judges who participated in the decision of this Court and to all the other available circuit judges of the circuit in regular active service, and no judge who

* Pursuant to Third Circuit I.O.P. 9.5.3., Judge Fuentes' vote is limited to panel rehearing.

concurred in the decision having asked for rehearing, and a majority of the judges of the circuit in regular service not having voted for rehearing, the petition for rehearing by the panel and the Court en banc, is denied.

BY THE COURT,

s/ Julio M. Fuentes
Circuit Judge

Dated: April 24, 2017
CJG/cc: All Counsel of Record

APPENDIX F

21 U.S.C. § 355

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. . . .

. . .

. . .

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . . or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the

labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

. . .

(k) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to

determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. . . .

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

. . .

(o) Postmarket studies and clinical trials; labeling

(1) In general

A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

. . .

(4) Safety labeling changes requested by Secretary

(A) New safety information

If the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

(B) Response to notification

Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under subsection (j) shall within 30 days--

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under subsection (j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) Review

Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.

(D) Discussions

Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless

the Secretary determines an extension of such discussion period is warranted.

(E) Order

Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under subsection (j) to make such a labeling change as the Secretary deems appropriate to address the new safety information. Within 15 days of such an order, the responsible person or the holder of the approved application under subsection (j) shall submit a supplement containing the labeling change.

(F) Dispute resolution

Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under subsection (j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

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. . .

. . .

21 CFR § 201.57

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA–approved patient labeling at the end of prescription

drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

. . .

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: "(Drug) is a (name of class) indicated for (indication(s))."

. . .

(9) Contraindications. A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings.

(10) Warnings and precautions. A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.

(11) Adverse reactions.

(i) A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).

. . .

. . .

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

. . .

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of

the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

. . .

(3) Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

. . .

(F) The usual duration of treatment when treatment duration should be limited,

. . .

. . .

. . .

(6) Warnings and precautions.

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of

the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

(ii) Other special care precautions. This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).

. . .

(7) Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug,

only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

(i) Listing of adverse reactions. This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be preceded by the information necessary to interpret the adverse reactions (e.g., for clinical trials, total number exposed, extent and nature of exposure).

(ii) Categorization of adverse reactions. Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be reliably determined, adverse reactions must be listed in decreasing order of severity.

(A) Clinical trials experience. This section must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse

reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be reliably determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified, if frequency ranges cannot be determined. For adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.

(B) Postmarketing experience. This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in clinical trials.

. . .

(9) Use in specific populations. This section must contain the following subsections:

. . .

(v) 8.5 Geriatric use.

. . .

. . .

(d) Format requirements. All labeling information required under paragraphs (a), (b), and (c) of this section must be printed in accordance with the following specifications:

(1) All headings and subheadings required by paragraphs (a) and (c) of this section must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Reverse type is not permitted as a form of highlighting.

(2) A horizontal line must separate the information required by paragraphs (a), (b), and (c) of this section.

(3) The headings listed in paragraphs (a)(5) through (a)(13) of this section must be presented in the center of a horizontal line.

(4) If there are multiple subheadings listed under paragraphs (a)(4) through (a)(13) of this section, each subheading must be preceded by a bullet point.

(5) The labeling information required by paragraphs (a)(1) through (a)(4), (a)(11)(ii) through (a)(11)(iv), and (a)(14) of this section must be in bold print.

(6) The letter height or type size for all labeling information, headings, and subheadings set forth in paragraphs (a), (b), and (c) of this section must be a minimum of 8 points, except for labeling information that is on or within the package from which the drug is to be dispensed, which must be a minimum of 6 points.

(7) The identifying numbers required by § 201.56(d) and paragraphs (c)(1) through (c)(18) of this section must be presented in bold print and must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type).

(8) The information required by paragraph (a) of this section, not including the information required under paragraph (a)(4) of this section, must be limited in length to an amount that, if printed in 2 columns on a standard sized piece of typing paper (8 1/2 by 11 inches), single spaced, in 8 point type with 1/2–inch margins on all sides and between columns, would fit on one-half of the page.

(9) Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the new or modified text.

(10) For the information required by paragraph (b) of this section, each section heading must be in bold print. Each subheading within a section must be indented and not bolded.

21 CFR § 314.70

(a) Changes to an approved NDA.

(1)(i) Except as provided in paragraph (a)(1)(ii) of this section, the applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a supplement under paragraph (b) or (c) of this section or by inclusion of the information in the annual report to the NDA under paragraph (d) of this section.

(ii) The submission and grant of a written request for an exception or alternative under § 201.26 of this chapter satisfies the applicable requirements in paragraphs (a) through (c) of this section. However, any grant of a request for an exception or alternative under § 201.26 of this chapter must be reported as part of the annual report to the NDA under paragraph (d) of this section.

(2) The NDA holder must assess the effects of the change before distributing a drug product made with a manufacturing change.

(3) Notwithstanding the requirements of paragraphs (b) and (c) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require

approval prior to distribution of the product or in an annual report).

(4) The applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) and (c) of this section.

(5) Except for a supplement providing for a change in the labeling, the applicant must include in each supplement and amendment to a supplement providing for a change under paragraph (b) or (c) of this section a statement certifying that a field copy has been provided in accordance with § 314.440(a)(4).

(6) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the submission.

(b) Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

(2) These changes include, but are not limited to:

. . .

(v) The following labeling changes:

(A) Changes in labeling, except those described in paragraphs (c)(6)(iii), (d)(2)(ix), or (d)(2)(x) of this section;

(B) If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter; and

(C) Any change to the information required by § 201.57(a) of this chapter, with the following exceptions that may be reported in an annual report under paragraph (d)(2)(x) of this section:

(1) Removal of a listed section(s) specified in § 201.57(a)(5) of this chapter; and

(2) Changes to the most recent revision date of the labeling as specified in § 201.57(a)(15) of this chapter.

. . .

(3) The applicant must obtain approval of a supplement from FDA prior to distribution of a drug product made using a change under paragraph (b) of this section. Except for submissions under paragraph (e) of this section, the following information must be contained in the supplement:

(i) A detailed description of the proposed change;

(ii) The drug product(s) involved;

(iii) The manufacturing site(s) or area(s) affected;

(iv) A description of the methods used and studies performed to assess the effects of the change;

(v) The data derived from such studies;

. . .

. . .

(c) Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).

(1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

. . .

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this

section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

. . .

(iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in § 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental NDA, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

. . .

21 C.F.R. § 314.80

(a) Definitions. The following definitions of terms apply to this section:

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including

the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

. . .

(b) Review of adverse drug experiences. Each applicant having an approved application under § 314.50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c) Reporting requirements. The applicant must submit to FDA adverse drug experience information as described in this section. . . .

. . .

(k) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

. . .

21 C.F.R. § 314.81

(a) Applicability. Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

. . .

(2) Annual report. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i) Summary. A brief summary of significant new information from the previous year that

might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

. . .

(iii) Labeling.

(a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under § 201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic

submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

. . .

(v) Nonclinical laboratory studies. Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) Clinical data.

(a) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored

series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(b) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(c) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

. . .

. . .

(d) Withdrawal of approval. If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

APPENDIX G

RESPONDENTS IN THIS PROCEEDING

Plaintiff	Appeal No.
Albrecht, Doris	14-1900
Molnar, Phyllis	14-2109
Molnar, William	14-2109
Gozdziak, Margaret	14-2110
Duke, Dolores	14-2111
Duke, Thomas	14-2111
Schultz, Susan	14-2112
Schultz, Russ	14-2112
Hines, Cynthia H.	14-2113
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Goodwin, Joan H.	14-2114
Moline, Barbara R.	14-2115
Moline, Ronald	14-2115
Wheeler, Kathryn K.	14-2117
Denker, Elayne	14-2118
Denker, Stephen	14-2118
Heaton, Nancy	14-2119
Bonne, Virginia	14-2120
Lefebvre, Alice	14-2121
Hogan, Marie	14-2122
Karch, Lillie	14-2123
Walraed, Susan	14-2124

Sullivan, J. Thomas	14-2124
Kolb, Lauren	14-2126
Kolb, Ralph	14-2126
Dematto, Mary E.	14-2127
Germino, Virginia Lee	14-2128
Chaires, Jeanette S.	14-2129
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Hodge, Helen	14-2163
Stark, Vivian	14-2164
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Voss, Eugene	14-2165
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Panouis, Androniki	14-2167
Blackford, June	14-2168
Krakovitz, Pearl	14-2169
Pisarz, Josephine	14-2170
Pisarz, Walter	14-2170
Strominger, Betty	14-2171
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Schick, John Charles	14-2172
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Price, Carolyn	14-2176
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Mayes, Claudice	14-2198
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Driver, William	14-2209
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Juth, Bernard S.	14-2210
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